THE JOURNAL OF
NERVOUS AND
MENTAL DISEASE

VOL. 180, NO. 7
July 1992
SERIAL NO. 1316

Clinical Correlates of Cerebral Ventricular Enlargement in Schizophrenia

Further Evidence for Frontal Lobe Disease

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Numerous studies have shown evidence of cerebral ventricular enlargement in schizophrenia and its relationship to severity of clinical symptoms and psychosocial dysfunction. In this large prospective study, 88 noninstitutionalized DSM-III-R schizophrenic patients were administered a CT scan and rated for positive and negative symptomatology and premorbid adjustment. The CT scans from 14 healthy controls were used for comparison of cerebral ventricular measures. Patients had an enlarged ventricle to brain ratio of the anterior portion of the lateral ventricles, the frontal horns, compared with controls. Patients with larger frontal horns had more severe negative symptoms and poorer premorbid childhood adjustment. The area of the main body of the cerebral lateral ventricles, though not elevated in patients, was correlated with the total number of prior hospitalizations. These results support the hypothesis of a structural and functional "frontal" deficit in schizophrenia.

— *J Nerv Ment Dis* 180:407–412, 1992

Disturbances in the frontal cortex have long been considered as a possible cause of schizophrenia. In 1919, Kraepelin proposed that a dysfunction of the frontal cortex was related to dementia praecox (Kraepelin, 1919/1971). Parfitt (1956) noted the similarities between 61 schizophrenic patients and other patients who had had a prefrontal leukotomy, concluding that deterioration or loss of frontal lobe function may lead to chronic schizophrenia. Kleist (1960), based on his observations of neurological patients, also proposed that some symptoms of schizophrenia were related to frontal lobe pathology.

Not until the advent of noninvasive computerized axial tomography (CT) were sufficient data available to demonstrate neuroanatomic disturbances in schizophrenia (Johnstone et al., 1976; Weinberger et al., 1979, 1982). In addition to these CT scan morphological findings, functional studies using regional cerebral blood flow (rCBF; Ingvar and Franzen, 1974) and positron emission tomography (PET; Buschbaum et al., 1982) have shown cerebral metabolic abnormalities of the frontal cortex in schizophrenic patients, leading some investigators to postulate a causal relationship between frontal lobe dysfunction and schizophrenia (Levin, 1984; Weinberger, 1984).

The clinical significance of these structural and functional abnormalities is not yet well understood. Several studies have shown relationships between ventricular enlargement and such clinical variables as negative symptomatology (Andreasen et al., 1982b, 1990a; Nasrallah et al., 1982; Williams et al., 1985), psychosocial deficits including poor premorbid adjustment (DeLisi et al., 1983; Weinberger et al., 1980a), response to treatment (Pandurangi et al., 1989; Smith et al., 1985; Weinberger et al., 1980b), and severity of illness and prognosis (Kolakowska et al., 1985; Pandurangi et al., 1988). There appears to be a group of patients characterized clinically by prominent negative symptomatology, poor response to treatment, chronic course of illness, intellectual impairment, and cerebral ventricular enlargement. Crow (1980) described this subtype as a type II syndrome or "deficit state". This deficit state may be

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related to anatomical deficits in the frontal lobe, because known neurological defects in the frontal cortex produce similar symptoms (Luria, 1980).

In this large prospective study of noninstitutionalized DSM-III-R schizophrenic patients, we report correlates of extensive clinical and psychosocial data with CT-determined neuromorphological findings. We evaluated the extent of ventricular enlargement in the frontal horns of the lateral ventricles and in the main body of the lateral ventricles, and examined whether clinical deficits were more strongly associated with atrophic changes in the anterior structures surrounding the frontal horns.

Methods

Subjects

From August 1986 to August 1989, 88 consecutive patients admitted to the Payne Whitney Clinic, New York, NY, with a DSM-III-R diagnosis of schizophrenia were recruited. All patients were younger than 55 years of age, had no known history of substance dependence, neurological disorder, metabolic disorder, or head injury, and gave informed consent. The subjects' average age (± SD) was 29.7 (± 7.7) years (range, 18 to 54 years), 54 (61%) were male, their mean duration of illness was 7.8 (± 6.6) years (range, 0 to 28 years), and their mean number of previous hospitalizations was 2.9 (± 3.3) (range, 0 to 15). Twenty-six patients had no previous hospitalizations. Patients taking neuroleptic medication at the time of admission were receiving an average of 440 (± 900) chlorpromazine (CPZ) equivalents per day, including one patient receiving 6650 CPZ equivalents.

The comparison group consisted of 14 age- and sex-matched patients from the Manhattan Eye, Ear, Nose, and Throat Hospital, New York, NY, receiving treatment for suspected eye trauma. These patients were referred to The New York Hospital for CT scans and had no known history of substance abuse, major psychiatric illness, neurological disorder, or metabolic disorder, or current medical illness. Eligible cases with eye trauma meeting our inclusion criteria over an 18-month-period were studied. Their average age was 28.1 (± 6.0) years and eight (57%) were male.

CT Scans

The CT scans were performed using a GE 8800 scanner collecting data transverse to the orbitomeatal line in 10-mm slices. Scoring of the scans was done independently by two neuroradiologists who had no knowledge of whether a subject was a patient or control. Scans demonstrating the largest area of the frontal horns of the lateral ventricles, main body of the lateral ventricles, and third ventricle were individually chosen by the two neuroradiologists and projected onto a screen. The areas were traced and subsequently measured three times on a Jandel Scientific digitizing tablet. The inner area of the skull on CT bone window projections corresponding to the selected slices was also traced.

After corrections for projection and enlargement, ventricle to brain ratios (VBRs) were calculated by dividing the mean ventricular area measurement (across the three measurements) by the area of the inner table of the skull. In this manner, the left, right, and total frontal horn and body of lateral ventricle VBRs and the VBR of the third ventricle were determined. Furthermore, the narrowest and widest widths of the third ventricle posterior to the interventricular foramen of Monro were identified and divided by the inner skull area to determine the narrowest and widest width ratio of the third ventricle. The left to right (L:R) ratios of ventricular area of the body and frontal horns of the lateral ventricles were also determined (Losonczy et al., 1986).

Interrater reliability was high for the frontal horns (.84) and for the body of the lateral ventricles (.89), but low for measurements of the third ventricle (.51 for the third ventricle area, .51 for the widest width of the third ventricle, and .46 for the narrowest width of the third ventricle). Based on the low interrater reliability for the third ventricle measurements, third ventricle indices were not included in statistical analyses.

Clinical Assessment

Patient assessment procedures included: a Structured Clinical Interview for DSM-III-R-Diagnosis (SCID-P) utilizing information gathered on admission and over the full course of hospitalization; Scales for Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS); Brief Psychiatric Rating Scale (BPRS); Global Assessment Scale (GAS) at admission and discharge; and Premorbid Adjustment Scale at discharge. The change in GAS score was utilized as an index of hospital treatment response.

Statistical Analysis

The primary goals of the study were: a) to detect differences in VBR measures between patients and controls, and b) to assess the relationships of ventricular morphology to clinical and psychosocial variables. Pearson correlations were used to assess the association between ventricular measures and clinical measures, and *t*-tests were used to compare patients and controls on the relevant VBR measures. Finally, one-way analysis of variance with post hoc paired comparisons were used to assess differences in CT scan measures across clinical subgroups (positive, negative, and mixed, as defined according to criteria proposed by

TABLE 1
Mean (± SD) Ventricle to Brain Ratios of Patients with DSM-III-R Schizophrenia and Controls

	Patients (N = 88)	Controls (N = 14)
VBR of frontal horns[a]	2.07 ± .79*	1.58 ± .53
VBR of lateral ventricles[b]	7.76 ± 2.57	7.08 ± 2.56
Left:right ratio of lateral ventricle VBRs	1.07 ± .21	1.04 ± .19

[a]Frontal horns, anterior horns of the lateral ventricles.
[b]Lateral ventricles, main body of the lateral ventricles.
*$p < .01$.

Andreasen et al., 1990b). The CPZ equivalents were determined for neuroleptic medications, and the logarithm of CPZ equivalents was used in correlational analyses to correct for the skewed distribution.

Results

CT Measurements of Patients vs Controls

As shown in Table 1 and Figure 1, there was a significant difference between schizophrenics and normal controls in the VBR measure of the frontal horns of the lateral ventricles (t = 2.84, df = 22.47, $p < .01$). The differences in the VBR measures of the body of the lateral ventricles and L:R ratio showed trends in the expected direction, but these did not reach statistical significance.

Clinical History

Correlations between clinical history variables and VBR measures are shown in Table 2. The frontal horn VBR correlated positively with age, duration of illness, and number of hospitalizations in the last 24 months. However, for patients less than or equal to 40 years of age (N = 82), the relationship between frontal horn VBR and age was not significant. When age was taken into consideration as a covariate, there were no significant relationships between the frontal horn VBR and duration of illness or number of hospitalizations in the past 24 months.

TABLE 2
Correlations between VBR Measures and Demographic and Clinical History Variables in 88 Schizophrenic Patients[a]

	FH VBR	LV VBR	L:R Ratio
Age	.22[b]*	.09	−.20*
Age at onset of illness	.00	−.04	−.09
Duration of illness	.26[c]*	.15	−.22[c]*
Total number of hospitalizations	.19	.24*	−.09
Number of hospitalizations in past 24 months	.20[c]*	.26[c]*	−.12

[a]Abbreviations used in this table: FH VBR, area of frontal horns (VBR); LV VBR, area of lateral ventricles (VBR); L:R Ratio, left:right ratio of lateral ventricle areas.
[b]Not significant for subjects with age less than or equal to 40 (r = .18, NS).
[c]Not significant with age used as a covariate.
*$p < .05$.

There was a positive correlation between VBR for the body of the lateral ventricles and the total number of hospitalizations (r = .24, $p < .05$). This relationship remained significant after considering age as a covariate and performing log transformation of the number of hospitalizations to correct for the skewed distribution. The L:R ratio showed a significant negative correlation with age (r = −.26, $p < .05$), persistent even when age was less than 40 years. There were no sex differences for any of the ventricular measurements.

Correlations between measures of premorbid adjustment and frontal horn VBR measures were as follows: childhood, r = .34, $p < .01$; early adolescence, r = .20; late adolescence, r = .17; adulthood, r = .14; and overall premorbid psychosocial adjustment, r = .05. There were no significant correlations between measures of premorbid adjustment and body of lateral ventricle or L:R ratio measures.

Clinical Symptomatology

As shown in Table 3, there were no significant correlations between any of the CT scan indices and positive symptoms (SAPS, BPRS) or GAS scores on admission. There were, however, significant correlations between negative symptoms (SANS total score) (r = .27, $p < .05$) and the frontal horn VBR measure, but not with lateral ventricle VBR or L:R ratio measures. Further

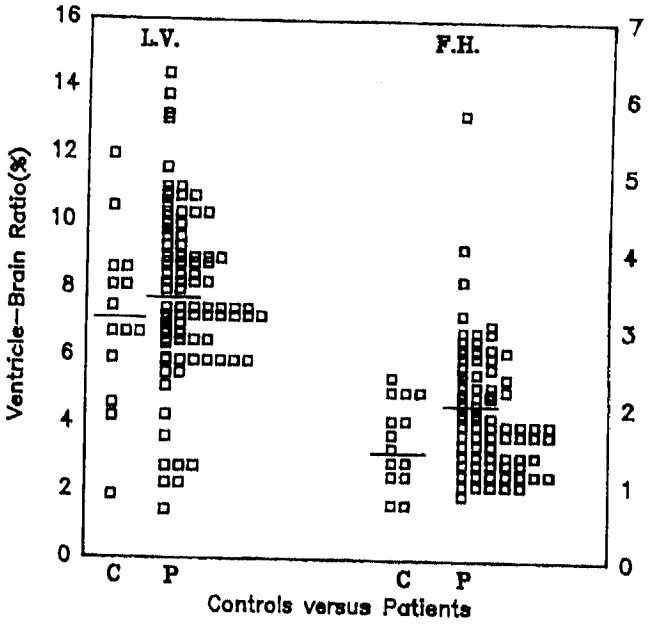

FIG. 1. Ventricle-brain ratio (%) of controls (C) versus patients (P) for the main body (LV) and frontal horns (FH) of the lateral ventricles. Solid bar indicates mean.

TABLE 3
Correlations Between Clinical Symptom Ratings and VBR Measures on Admission[a]

	N	FH VBR	LV VBR	L:R Ratio
Positive Symptoms	73			
Hallucinations		.03	−.22	.00
Delusions		−.05	−.17	.14
Thought disorder		−.11	−.04	.04
Bizarre behavior		.14	.11	.05
SAPS (total score)		.01	−.14	.09
Negative Symptoms	53			
Alogia		.16	.03	.18
Avolition		−.03	.04	.27
Anhedonia		.36**	.22	.08
Affective flattening		.33*	.16	.09
Attentional impairment		.09	−.08	.02
SANS (total score)		.27*	.11	.19
BPRS (total score)	73	.16	−.07	.02
GAS	78	.11	.16	−.19

[a]Abbreviations used in this table: FH VBR, area of frontal horns (VBR); LV VBR, area of lateral ventricles (VBR); L:R Ratio, left:right ratio of lateral ventricle areas.
*$p < .05$.
**$p < .01$.

TABLE 4
Mean (± SD) VBR Measures for Positive, Negative, and Mixed Clinical Subtypes of Schizophrenic Patients[a]

	N	FH VBR	LV VBR	L:R Ratio
Positive subtype	10	2.05 ± .60	7.41 ± 2.01[b,c]	1.07 ± .26
Mixed subtype	36	2.17 ± .74	8.36 ± 2.30	1.09 ± .23
Negative subtype	6	2.56 ± 1.62	9.55 ± 2.27	1.07 ± .14

[a]Abbreviations used in this table: FH VBR, area of frontal horns (VBR); LV VBR, area of lateral ventricles (VBR); L:R Ratio, left:right ratio of lateral ventricle areas.
[b]Versus negative-symptom group, $p < .07$.
[c]Trend analysis for positive-, mixed-, and negative-symptom group, $p < .07$.

analysis of SANS subscales indicated that correlations were significant for anhedonia ($r = .36$, $p < .01$) and affective flattening ($r = .33$, $p < .05$). Subdividing patients into clinical subtype groups based on symptoms at admission (according to the criteria described by Andreasen et al., 1990b) produced the results shown in Table 4. Patients with prominent negative symptoms tended to have larger mean VBR of the lateral ventricles than those with positive ($t = 1.97$, $df = 14$, $p < .07$) symptoms. There were no significant differences in the L:R ratio among symptom groups.

There were significant negative correlations between the frontal horn VBR and GAS scores at discharge ($r = -.31$, $p < .05$) and change in GAS score from admission to discharge ($r = -.27$, $p < .05$), which indicates that frontal horn enlargement was associated with poorer overall functioning at discharge and poorer hospital treatment response. There were no significant correlations between either frontal horn or lateral ventricle VBR measures and positive or negative symptoms, BPRS, or neuroleptic dose at discharge.

Discussion

The differences in ventricular morphology between schizophrenic patients and normal controls have been described previously in the literature (Johnstone et al., 1976; Weinberger et al., 1979, 1982). Our finding of significantly larger frontal horns of the lateral ventricles in schizophrenic patients extends these observations in a large and carefully diagnosed noninstitutionalized population, and is consistent with a recent report by Andreasen et al. (1990a) demonstrating frontal horn enlargement by magnetic resonance imaging in a smaller cohort. The observation of significant group differences in frontal horn area, but not lateral ventricle area, suggests that disorder-related atrophic changes are more prominent in the areas surrounding the frontal horns. However, the sample of control subjects is too small to exclude the existence of any lateral ventricle enlargement in our patients.

The correlations between VBR measures and clinical history variables showed that there was no relationship between ventricular enlargement and age when patients over 40 years of age were excluded from the analysis, nor was there an association with duration of illness when age was used as a covariate. There appeared to be, however, a relationship between lateral ventricular size and total number of hospitalizations. This most likely reflects a relationship based on severity or intermittent course of illness, rather than effects of hospitalization. The majority of CT studies of ventricular enlargement in schizophrenia have shown no association between VBR and duration of illness or number of hospitalizations (Johnstone et al., 1976; Nasrallah et al., 1983; Weinberger et al., 1979), although studies to the contrary do exist (Kemali et al., 1989). There were no sex differences in any of the VBR measures.

Patients with larger frontal horns had higher childhood premorbid maladjustment scores. This is in direct support of previous work demonstrating a significant negative correlation between childhood adjustment scores and ventricular enlargement (DeLisi et al., 1983; Weinberger et al., 1980a), and suggests that cases with enlarged VBR have functional deficits from an early point in life. This observation raises the possibility that frontal cortical changes begin early in life in some cases. Such changes may reflect an early neurodevelopmental abnormality, possibly of genetic origin or as a result of CNS trauma. The observation also indicates that frontal cortical dysfunction may be associated with significant behavioral impairments, even well before actual symptom onset.

Ventricular enlargement, particularly in the frontal horns, was associated with more severe negative symptoms. The associations were strongest with anhedonia and affective flattening. This finding is consistent with some earlier work demonstrating a relationship between ventricular enlargement and negative symptomatology (Andreasen et al., 1982b, 1990a; Nasrallah et al., 1982; Williams et al., 1985), although other attempts to demonstrate this relationship have not all been successful (*e.g.*, Losonczy et al., 1986; Nasrallah et al., 1983). Our success in demonstrating associations between ventricular enlargement and clinical deficit characteristics in the present study may be due, in part, to certain methodological features of this investigation. In particular, measurement of the frontal horn of the lateral ventricle could be a particularly important ventricular area because of its proximity to frontal cortical structures. Frontal lobe deficits are thought to cause negative symptoms, such as flat affect, diminished motivation, and alogia (Luria, 1980). Second, our assessment of negative symptoms shortly after admission to hospital, before neuroleptic doses were significantly increased during hospitalization, might have been important because extrapyramidal symptoms such as akinesia can mimic negative symptoms and thereby confound assessment of disease-related behavioral deficits.

Previous studies on the relationship between ventricular enlargement and treatment response have yielded equivocal findings. Some studies have shown a strong correlation (Pandurangi et al., 1989; Weinberger et al., 1980b), while others have shown no association (Losonczy et al., 1986). In one report, the prognosis was actually better in patients with enlarged ventricles (Smith et al., 1985). In our study, GAS score at discharge and change in GAS score from admission were negatively correlated with VBR measurements. Patients with larger ventricles showed less change in GAS score and a lower GAS score at the time of discharge. This association of VBR enlargement with poor global outcome is consistent with earlier work indicating that first episode schizophreniform patients with large VBRs had poorer global outcome as determined by GAS score than those with normal ventricular size (DeLisi et al., 1983).

Our observations suggest that there is a structural frontal lobe deficit in schizophrenia that may explain some of the behavioral manifestations of the disease, particularly those related to the higher cognitive and affective functions. Knowing that the frontal cortex is involved in motivation, affect, and speech—principal areas of function affected in schizophrenia—the hypothesis of frontal lobe dysfunction in schizophrenia appears all the more tenable an explanation for at least some aspects of the disease process.

Conclusion

The etiology of schizophrenia remains unknown. Prospective family studies and twin studies support the notion of a congenital defect; however, its manifestation may be dependent on exposure to psychosocial and/or physical environmental factors (Crow, 1987). Cerebral ventricular enlargement often is found at the onset of disease (Weinberger et al., 1982), and earlier studies suggest that VBR does not increase with disease progression (Illowsky et al., 1988; Nasrallah et al., 1986). Cerebral ventricular enlargement may represent the dropout of periventricular fibers during development, which might result from a genetic factor or prenatal or perinatal insult. The association between cerebral ventricular enlargement and poor childhood psychosocial adjustment in our study suggests that neuroanatomic abnormalities of frontal cortex may show developmental progression from early in life, and that such changes are associated with early psychosocial developmental deficits.

Our findings of greater frontal ventricular enlargement in association with negative or "frontal" symptomatology give support for the hypothesis of a structural and functional frontal deficit in schizophrenia. Imaging studies using rCBF, PET and magnetic resonance imaging also suggest a deficit in the frontal cortex in schizophrenia (Andreasen et al., 1986; Buschbaum et al., 1982; Ingvar and Franzen, 1974). Our findings add to this area of research by demonstrating that: a) enlargement in the area of frontal horns was greater than enlargement in the main body of lateral ventricles, and b) frontal horn enlargement was related to negative, but not positive, symptoms, early deficits in psychosocial adjustment, severity of illness, and diminished treatment response. The observation of greater correlations of behavioral deficits with enlargement of the frontal horns than of the main body of the lateral ventricles is consistent with our earlier observations (Keilp et al., 1988) and those of Andreasen et al. (1990a). The specificity of frontal lobe anatomical abnormalities, in association with behavioral correlates, further implicates frontal lobe dysfunction in the pathogenesis of schizophrenia.

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