Enlarged Cerebral Ventricles in Schizophrenia

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A substantial body of neuroradiological evidence, including 50 years of pneumoencephalographic (PEG) studies, as well as more recent investigations with computed tomography (CT), indicates that some chronic schizophrenic patients have structural brain abnormalities. The evidence from the CT studies is most consistent with mild cerebral atrophy. In most studies, chronic schizophrenic patients as a group have been found to have significantly larger cerebral ventricles than healthy control subjects,\(^1\)\(^2\) than normal controls drawn from the literature,\(^3\)\(^4\) and than their own non-schizophrenic siblings.\(^5\) These patients may also be more likely to have dilated cortical fissures and sulci than control subjects\(^6\) and are more likely to have reversals of the usual frontal and occipital lobe asymmetries.\(^7\)\(^8\) A small percentage (probably less than 10%) have apparent atrophy of the anterior cerebellar vermis.\(^9\)\(^10\) Finally, Golden et al.\(^11\)\(^12\) found significantly reduced CT numbers—a measure related to parenchymal density—in a small group of schizophrenic patients as compared with control subjects.

Of the various abnormalities reported, ventricular enlargement appears to be the most compelling. The other findings have been less consistently replicated, and occur less frequently. Ventricular enlargement, on the other hand, was observed in most of the early PEG studies and has now been found in over 15 controlled CT studies. Furthermore, there is some evidence that ventricular enlargement is correlated with other clinical and biological variables which have been considered important in understanding schizophrenia. For these reasons, it may prove to be a useful marker for perhaps some forms of this disorder.

THE MEANING OF VENTRICULAR ENLARGEMENT

Cerebral ventricular enlargement is a non-specific alteration in gross brain structure, the end result of numerous pathological processes and even more numerous etiologies. It is a biological marker of a past or present brain disorder, usually one involving either degeneration of brain tissue or obstruction to cerebrospinal fluid circulation. Ventricular enlargement on a CT scan is taken as such a marker, although a few recent case reports of apparent reversal of cortical atrophy suggest that all that is atrophy on a CT scan may not be true atrophy of the brain.\(^3\) That some chronic schizophrenic patients have enlarged cerebral ventricles on CT scans seems no longer a matter of question. The accompanying figure is a dramatic example of this fact.

It is also reasonably certain that one is more likely to find an individual with enlarged ventricles among a sample of chronic schizophrenic patients than among a similarly aged group of healthy individuals.\(^3\) What is uncertain, however, is whether enlarged ventricles are relevant in terms of pathogenesis, clinical phenomenology, or prognosis to the schizophrenic illness in those individuals who have this finding, or whether it is an artifact or epiphenomenon. It is possible, for example, that environmental factors such as institutionalization or somatic therapies produce enlarged ventricles. Although this possibility is difficult to dismiss conclusively, as previously discussed, the data weigh against it.\(^3\) Since enlarged ventricles also are found in a small percentage of first episode schizophreniform patients, it cannot be exclusively the result of treatment.

Before considering what the relevance of ventricular enlargement may be, we should note what clearly it is not. The finding has no diagnostic significance. Most chronic schizophrenic patients have normal-sized ventricles. In our original series of 80 severely ill patients, less than one-third had ventricles larger than the largest of 66 normal control subjects.\(^3\) Furthermore, only a very small fraction of all individuals with large ventricles are likely to be schizophrenic. Some are probably "normal." Even among psychiatric patients, ventricular enlargement is not specific to schizophrenia and has been found in some patients with affective disorders.\(^4\) It is for these reasons that CT scanning has no clinical application in psychiatry at the present time, except to rule out certain neurological...
conditions. All of this brings us to the question of whether ventricular size has a role as a meaningful biological marker in schizophrenia research. In response to this question, we would agree with Melzer, who wrote, "The issue, then, is not whether the specific abnormality is a marker for schizophrenia or affective illness but to demonstrate that the abnormality in question is relevant to the psychopathology of the individuals in whom it is present." A useful medical analogy is the case of hypertension and kidney disease. If we were studying renal disease and knew nothing about its association with hypertension, we might be inclined to disregard the latter condition because it is non-specific, it is found in association with many other medical conditions, and it occurs in asymptomatic, normal individuals. One way to approach this issue in the case of ventricular enlargement is to see whether the finding correlates with other potentially meaningful variables related to schizophrenia.

CORRELATES OF VENTRICULAR ENLARGEMENT IN SCHIZOPHRENIA

The evidence supporting a relationship between enlarged ventricles and the psychopathology of those individuals who have this abnormality is multidimensional. Much of it, however, is preliminary and in need of replication.

NEGATIVE SYMPTOMS

In their study of 17 chronic schizophrenic patients, Johnstone et al. found an association between enlarged ventriciles and "negative" clinical features, i.e., affective flattening, retardation, and poverty of speech. A more recent study by Andreassen et al. produced similar findings. Studying negative symptoms is difficult because they are not easily quantified and isolated. Nevertheless, as will be mentioned later, there is considerable overlap between variables generally associated with negative symptoms and those correlated with enlarged ventriciles.

NEUROPSYCHOLOGICAL IMPAIRMENT

Five studies of schizophrenic patients have found a significant relationship between ventricular size and performance on neuropsychological tests. Johnstone et al. observed this with the Withers and Hinton Battery, Famuyiwa et al. with the paired associative learning test. Donnelly et al. and Adams et al. utilized the Halstead-Reitan Battery, and Golden et al. found a very high multiple correlation of 0.72 for ventricular size and scores on the Luria Neuropsychological Test Battery. These findings are consistent with the notion that the enlarged ventricles seen on the CT scans of schizophrenic patients represent a functionally meaningful brain abnormality.

Since the Donnelly et al. report, we have expanded our series to 23 patients who have completed the Halstead-Reitan Battery. Eleven of these patients had CT evidence of atrophy (10 enlarged ventricles—defined as ventricular size greater than two S.D. of the previously studied group of normal controls), and one had cortical atrophy without enlarged ventricles). The two groups did not differ significantly for age, age at onset of illness, length of illness, duration of hospitalization and years of education. Table 1 shows the results based on the Average Impairment Rating (AIR), a measure of overall test performance.

Table 1 illustrates two points. First, the patients with the CT findings had significantly greater deficits. And second, they performed more homogeneously; it being very unlikely that a patient with enlarged ventricles would score in the normal range (AIR>1.55).

CLINICAL NEUROLOGICAL SIGNS

Chronic schizophrenic patients frequently manifest nonspecific clinical signs of neurological dysfunction. Two of these signs, disordered smooth pursuit eye movements and non-focal, so-called "soft signs," may be more apparent in patients with enlarged cerebroventricular. Using a 12-item inventory of clinical "soft signs" and a pendulum eye-tracking paradigm analogous to that described by Holzman et al., we compared a group of chronic schizophrenic patients with enlarged ventricles with patients with normal CT scans. The oculographic eye-tracking records were rated blindly using a five-point reference scale. Despite considerable overlap, the patients with the CT scan abnormalities had more soft signs and more disordered eye movements (Table 2). In addition, in the eye-tracking task, nine of the 14 patients with large ventricles had markedly disordered tracking (a rating of >3) as compared with only six of the 20 patients with normal ventricles (p<.05, chi square).

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PREMORBID ADJUSTMENT

Of all the clinical features of schizophrenia, perhaps none has greater prognostic value than premortem social adjustment. In a retrospective blind study of 51 chronic schizophrenic patients, we compared the premortem adjustment of 19 patients with enlarged ventricles with that of 32 patients with normal ventricles. Despite a study sample biased toward poor premortem adjustment, we found global and early childhood adjustment to be significantly poorer in the group with large ventricles. Furthermore, of the nine patients with the poorest adjustment scores during childhood, all had abnormal CT scans while only three of the 13 patients with the best adjustment had abnormal scans (p<.001, Fisher Exact). This finding suggests that either poor premortem schizophrenic patients are somehow at greater risk for developing enlarged ventricles or that ventricular enlargement in such patients is a marker for an early developmental brain disorder that interferes with normal social maturation. The finding that some patients have enlarged ventricles at the onset of their illness lends support to the latter possibility. It further suggests that enlarged ventricles predate the onset of the psychotic symptoms during late adolescence.

RESPONSE TO TREATMENT

All of the correlations with enlarged ventricles mentioned thus far have in common an association with poor prognosis. It is reasonable to consider, therefore, whether ventricular enlargement has prognostic significance. In a blind, controlled study of 20 chronic schizophrenic patients, 10 of whom had enlarged ventricles, we compared the response to neuroleptic drug treatment of these two groups. The study design involved four weeks off all medication and eight weeks of standard neuroleptic therapy. The change in BPRS scores between the completion of the medication-free period and the end of the study reflected treatment response. The patient groups did not differ significantly in age, age at onset of illness, years of illness, years of hospitalization, neuroleptic dosage, or plasma neuroleptic concentrations. Furthermore, there was no significant difference in the drug-free psychopathology (BPRS) ratings between patients with normal ventricles (mean ± S.D. 59.5 ± 20.5) and patients with enlarged ventricles (51.7 ± 21.2). After neuroleptic therapy, however, the former group was significantly less symptomatic (31.9 ± 10.7) than the latter (51.4 ± 16.9) (p<.01). Response to treatment, as reflected in the change in BPRS scores, in the group with enlarged ventricles (0.3 ± 16.0) was thus significantly poorer (p<.01) than in the group with normal ventricles (27.5 ± 19.2).

VENTRICULAR ENLARGEMENT AND THE Dopamine HYPOTHESIS

The finding that chronic schizophrenic patients with enlarged ventricles may be poor neuroleptic responders

XANAX Tablets © (alprazolam)

CONTRAINDICATIONS

Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS

Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause lethal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS

General: If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs. (b) possible fetal abnormalities. (c) operating machinery or driving. (d) not increasing dose of the drug due to risk of dependence. (e) not stopping the drug abruptly. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. Drug/Laboratory Test Interactions: No consistent pattern for a specific drug or specific test. Carcinogenicity: Malignant. Impairment of Fertility: No carcinogenic potential or impairment of fertility in rats. Pregnancy: See Warnings. Nontoxic Effects: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. Labor and Delivery: No established use. Nursing Mothers: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. Pediatric Use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness. Central Nervous System: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. Cardiovascular: Tachycardia/palpitations, and hypotension. Sensory: Blurred vision. Musculoskeletal: Rigidity and tremor. Cutaneous: Dermatitis/allergy. Other Side Effects: Nasal congestion, weight gain, and weight loss. In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritis, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analyses are advisable. Minor EEG changes of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. After prolonged therapy dosage should be tapered Controlled Substance Class: XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

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TABLE 2
VENTRICULAR SIZE AND NEUROLOGICAL SIGNS

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<tr>
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<th>CT Normal</th>
<th>CT Abnormal</th>
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<tr>
<td>Non-Focal Signs</td>
<td>1.1 ± 1.0</td>
<td>2.4 ± 2.0*</td>
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<tr>
<td>(N=20)</td>
<td></td>
<td>(N=20)</td>
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<tr>
<td>Eye Tracking</td>
<td>2.5 ± .71</td>
<td>3.2 ± .75**</td>
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<tr>
<td>(N=20)</td>
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<td>(N=14)</td>
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*p = .01
**p < .05

Figure. Example of CT scan in horizontal and coronal (upper image) section showing dramatic ventricular enlargement in a 24-year-old chronic schizophrenic male.

has implications for the dopamine hypothesis of schizophrenia. This hypothesis, although of major heuristic value and central to research in the field, is not supported by much of the biological data about schizophrenic patients. One of the problems with testing this hypothesis may be the biological heterogeneity characteristic of schizophrenia. If, for example, patients with enlarged ventricles are a group for whom dopaminergic hyperactivity is not a relevant pathogenic factor, as suggested by their resistance to dopamine-blocking drugs (neuroleptics), then excluding these patients from tests of the dopamine hypothesis may prove more productive.

There is some data in addition to drug response to support this research strategy and to suggest that the dopamine hypothesis may be more relevant for schizophrenic patients with normal ventricles. Alpha-methyl-p-tyrosine (metyrosine), a dopamine synthesis inhibitor, has been found to potentiate the therapeutic effects of neuroleptics. Nasrallah et al.29 who had been unable to replicate this, later reported that six of seven metyrosine non-responders had cerebral ventricular enlargement. Drugs with dopamine agonistic properties might also be expected to affect patients differently depending upon their ventricular size. Jeste et al.30 studied the response to subcutaneous apomorphine given blindly to seven chronic schizophrenic patients. Three patients showed no change, while four were transiently affected (one improved while three worsened). All three non-responders had large ventricles; the other four patients had ventricles of normal size. In a related study, Angrist et al.31 reported that positive symptoms in chronic schizophrenic patients were more likely to improve with neuroleptics and to worsen with amphetamine than were negative symptoms. If, as Johnstone et al.17 has suggested, negative symptoms are more characteristic of patients with large ventricles, this would be consistent with the other reports.

Another approach to the dopamine hypothesis has recently been described by Kleinman et al.32 They found that prolactin levels in unmedicated patients correlated inversely with degree of psychopathology as reflected in BPRS scores, but only if the patients had normal ventricles. Large ventricle patients showed no such correlation. Studies of spontaneous blink rates (a possible marker of dopaminergic activity), changes in blinking with dopaminergic agents, and the relationship between blink rates and psychopathology are also consistent with the notion that patients with large ventricles do not fit the dopamine hypothesis as well as other patients. Finally, attempts to correlate ventricular size with biogenic amine levels or the activity of related enzymes in body fluids (e.g., platelet monoamine oxidase (MAO), urinary phenyl-ethylamine, plasma dopamine-β-hydroxylase (DBH) thus far have been unsuccessful.33

CONCLUSIONS
The results of the studies cited suggest that ventricular enlargement in schizophrenia, despite its non-specific nature, is a marker of a more homogeneous sub-group of patients with this illness. While the prevalence of this subgroup is unknown, it is certainly a minority of patients. Even so, in the absence of more definitive knowledge about the pathogenesis and etiologies of the schizophrenic syndrome, ventricular enlargement is a lead worth pursuing. The fact that a structural brain abnormality is associated with any cases of schizophrenia has implications for our understanding of the syndrome. It may lead not only to a clearer sense that schizophrenia is a non-specific syndrome, but also to identifying etiologically more homogeneous populations. Crow
recently proposed that current research in schizophrenia supports a division of the syndrome into two overlapping dimensions, which he calls Type I and Type II. Combining his proposal with the work already mentioned, these dimensions can be expanded as shown in Table 3. Ventricular enlargement appears to be associated with the Type II dimension.

REFERENCES


<p>| TABLE 3 |
| DIMENSIONS OF THE SCHIZOPHRENIC SYNDROME |</p>
<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
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<tr>
<td>Characteristic Symptoms</td>
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<td>Course</td>
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