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ORIGINAL PAPER

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Asymmetry of the ventricle and age at the onset of schizophrenia

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Abstract The relationship between lateral ventricular size or its asymmetry and age at the onset of schizophrenia was investigated in 20 schizophrenic patients diagnosed according to DSM-III-R criteria. The ventricle-brain ratio (VBR) was determined using three transaxial slices of magnetic resonance image (MRI) and asymmetry of the lateral ventricle was evaluated from the laterality index of the lateral ventricular area: (left – right/ left + right) × 100. Each age at the onset of the prodromal and active phase according to DSM-III-R criteria was determined for each patient. The results showed that asymmetry of the ventricle, but not VBR, was significantly correlated inversely with age at the onset of both the prodromal phase and active phase. Neither asymmetry nor VBR correlated with the duration of illness, age at MRI scanning, or severity of clinical symptoms. It would thus appear that greater asymmetry of the ventricle is associated with earlier onset of schizophrenia.

Key words Magnetic resonance imaging · Schizophrenia · Asymmetry of the lateral ventricle · Age at the onset of illness

Introduction

Computerized tomography (CT) and magnetic resonance imaging (MRI) have demonstrated relative ventricular enlargement at least in a subgroup of patients with schizophrenia (Johnstone et al. 1976; Kelsoe et al. 1988). Ventricular enlargement was reported to be present early in the course of the disease (Andreasen et al. 1990; Weinberger et al. 1982), and several follow-up studies have indicated ventricular change to be nonprogressive in schizophrenic patients as a group (Illowsky et al. 1988; Vita et al. 1988). Ventricular enlargement has been found greater on the left than right side in some schizophrenic patients (Crow et al. 1989a; DeLisi et al. 1991; Losonczy et al. 1986), and more frequent in male than female patients (Andreasen et al. 1990). Onset of schizophrenia is approximately 5 years earlier in male patients than female patients (Loranger 1984).

These findings suggest that ventricular enlargement or its asymmetry may be associated with age at the onset of schizophrenia. To our knowledge, however, few reports have been published on this issue. Several studies have found no correlation between ventricle-brain ratio (VBR; LaFosse et al. 1994; Mozley et al. 1994) or bilateral ventricular size and age at the onset of symptoms (Suddath et al. 1990). Only one study (DeLisi et al. 1991) found age at the first behavioral change in first-episode schizophrenic-like patients to be inversely correlated with left ventricular size as determined using MRI. Another study (Crow et al. 1989b) reported that ventricular horn size or its asymmetry assessed at CT scan was not distinguished by an earlier age of onset.

The purpose of the present study is to examine the relationship between lateral ventricular size or its asymmetry and age at the onset of schizophrenia using a more quantitative method: Each age at the onset of the prodromal and the active phase of schizophrenia was determined according to DSM-III-R criteria, and asymmetry of the ventricle was evaluated using the laterality index.

Subjects and methods

An initial total of 27 patients meeting DSM-III-R criteria for schizophrenia and who gave informed consent for the examination entered the study. The subjects were in- or outpatients of Toyama Medical and Pharmaceutical University Hospital and all had been treated with neuroleptics at MRI scanning. Only subjects under age 40 years were selected to eliminate possible effects of aging. Subjects were excluded if they had a history of any organic mental disorder, alcohol abuse, neurologic disease, or drug treatment known to affect the brain (e.g., cortisol). Of 27 patients, 7 were excluded because of lateral tilting of the head assessed by the method

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of Zipursky et al. (1990). The data of the remaining 20 patients were thus included for analysis. Seven were male and 13 female; 18 subjects were right-handed and two left-handed.

Age at the onset of the prodromal phase and active phase was determined according to DSM-III-R criteria by one of the authors (M.S.) blind to the MRI results. Mean (± SD) age at the time of MRI scanning was 22.3 (± 4.1) years (range 15.9–29.6 years). Mean age at the onset of the prodromal phase was 17.8 (± 3.5) years (range 13–26 years), and the onset of the active phase was 19.0 (± 3.2) years (range 14.3–26.0 years). Mean duration of illness, defined as the period that had elapsed since the onset of the prodromal phase, was 4.5 (± 3.2) years (range 0.5–11.6 years). There were no significant differences between male and female patients in age at the onset of prodromal or active phase. Severity of clinical symptoms were determined using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1984) and the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987).

MRI procedures

Magnetic resonance imaging (MRI) scans were performed using a Siemens Magnetom 1.5 Tesla scanner. All patients were aligned in the MRI scanner using the laser alignment system to avoid lateral tilting of the head. Some T2-weighted slices (repetition time 2500 ms; echo time 90 ms) were obtained. The transaxial slices were oriented so as to be parallel to the superior orbitomeatal line on the scout midsagittal image. Slice thickness was 7 mm and the slices were separated by 1.4 mm. Images from MRI films were converted to a computer system (Macintosh IIci, Apple Computer Inc., Cupertino, California, USA) using CCD video camera, light viewbox, and graphics display board (RasterOps 24STV, RasterOps Corporation, Santa Clara, California, USA). Quantitative measurements of regions of interest were made with the NIMH Image 1.35 software program.

Lateral tilting of the head of patients during the MRI scanning procedure was assessed according to the method of Zipursky et al. (1990). Areas of the intracranial space were measured using seven contiguous transaxial T2-weighted slices. Then the slopes, derived from the individual plots of section number vs log (the area of the left intracranial space/the area of the right intracranial space), were calculated. Of 27 patients, 7 were excluded because they showed significant slopes ($P < 0.01$; Pearson's product-moment correlations). In the remaining eligible 20 subjects, data from three contiguous slices in which anterior horns, body, and posterior horns were seen at their maximum were analyzed. The ventricle-brain ratio (VBR) was determined as follows: VBR = sum of the areas of bilateral ventricle in three slices/sum of the area of intracranial space in three slices × 100.

Asymmetry of the ventricle was evaluated based on the absolute value of the laterality index of the lateral ventricular area in the three slices: (left – right)/(left + right) × 100.

Correlation between MRI measurements and clinical variables were assessed using Pearson's product-moment correlations.

Results

Of 20 subjects, 19 showed larger left lateral ventricles relative to right ventricles. As shown in Fig. 1, significant negative correlations were found between the absolute value of the laterality index of the ventricle and age at the onset of the prodromal phase ($r = -0.501$; $P = 0.0243$) and active phase ($r = -0.529$; $P = 0.0160$). The VBR (4.47 ± 1.56; range 2.26–8.43) did not correlate with age at the onset of the prodromal or active phase. Neither laterality index of the ventricle nor VBR correlated with age at MRI scanning or the duration of illness. No significant differences in male and female patients with regard to the laterality index of the ventricle or VBR were found.

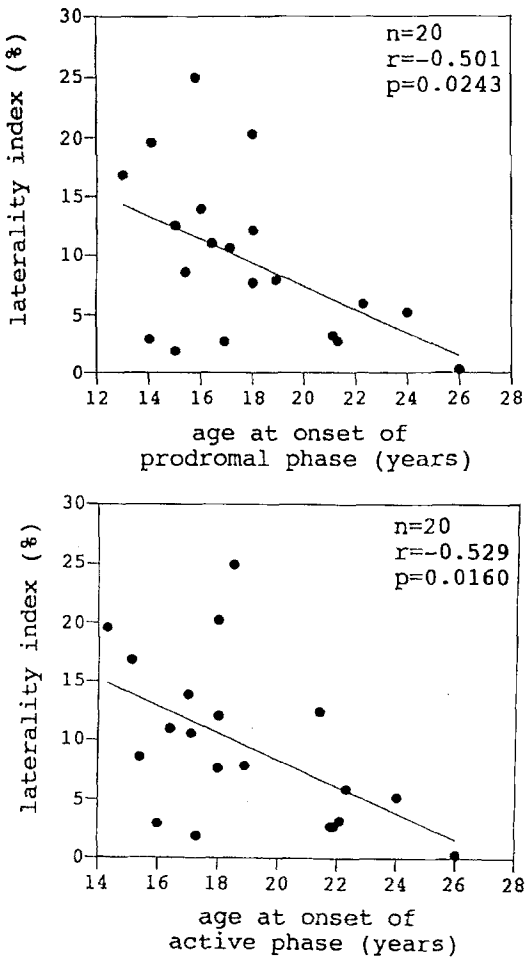

Fig. 1 Correlation of laterality index of the ventricle with age at the onset of the prodromal phase *(top)* and active phase of schizophrenia *(bottom)*. Laterality index of the ventricle was assessed using the absolute value of the index of ventricular area: (left – right)/(left + right) × 100. The r indicates Pearson's product-moment correlation coefficient

A significant positive correlation was found between the duration of illness and the age at MRI scanning ($r = 0.563$; $P = 0.0098$). The duration of illness did not correlate with age at the onset of prodromal or active phase.

Severity of clinical symptoms determined with the composite score of SANS (58.3 ± 22.6) and the PANSS (positive symptoms 13.4 ± 3.8; negative symptoms 12.7 ± 4.0; general psychpathology 10.7 ± 2.2) did not correlate with the laterality index of the ventricle or VBR.

Discussion

In the present study VBR did not correlate with age at the onset of the prodromal or the active phase in schizophrenic patients, corroborating other findings (LaFosse et al. 1994; Mozley et al. 1994; Suddath et al. 1990). The laterality index of the ventricle was, however, significantly correlated inversely with age at the onset of both the prodromal and active phases. This finding is in accordance

with the report of DeLisi et al. (1991), but at variance with that of Crow et al. (1989b). In the study by Crow et al., however, only the anterior and posterior horn areas were measured using the CT scan, and the subjects were of an advanced age (mean age 56 years). The discrepancies thus may have been due to the methods of measurement and the age of the subjects. Asymmetry, rather than the size of the lateral ventricle, would therefore seem to be relevant to the time of onset of the schizophrenic symptoms.

Ventricular enlargement most probably antedates the onset of symptoms, because this has been reported to be present early in the course of the disease and associated with poor premorbid adjustment and poor diagnostic outcome of schizophreniform disorders (Weinberger et al. 1980; Vita et al. 1991; DeLisi et al. 1992). Consistent with this view, laterality index of the ventricle in the present study was not correlated with the duration of illness or age at the time of MRI scanning. These structural changes in brain of schizophrenic patients may have their origin in development as suggested by the finding of no accompaniment of glial reaction (Crow et al. 1989a), and asymmetry of the ventricle might reflect the arrest of lateralized development (Crow et al. 1989a).

Patients with early onset have been reported to have significant reductions in the width of the left hemisphere in measures taken in the occipital and temporal regions (Crow et al. 1989b, 1990). Our subsequent MRI studies (Aso et al. 1994) revealed the volume of the anterior part of the left, but not right, medial temporal structure to be signifcantly ($P < 0.01$) correlated with age at the onset of the prodromal phase. These findings are consistent with the view that asymmetry of the ventricle or slight morphologic changes in the left hemisphere underlie vulnerability that give rise to schizophrenic symptoms.

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