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Stereological Volumetry of Cerebral Hemispheres and Lateral Ventricles Using MRI in Schizophrenia Subtypes

Background/Objectives: The structural changes of brain (cerebral and lateral ventricles volumes) in schizophrenia are controversial. This is partly due to the heterogenicity of the schizophrenia subtypes. In this study we compared the changes in the volumes of cerebral hemispheres and lateral ventricles in 3 subtypes of schizophrenia (paranoid, undifferentiated and residual) with normal controls.

Materials and Methods: 29 schizophrenia patients (21 men, 8 women) of 3 subtypes of paranoid, undifferentiated, and residual (according to DMS-IV criteria) were compared with 29 age- and gender-matched normal controls. All cases and controls underwent 3-D brain MRI of full coronal series, 1.5 mm slices without interslice gaps. The hemispheres and lateral ventricles were outlined and their volumes were calculated using Cavalieri's Principle. The results were statistically analyzed.

Results: The brain was slightly but insignificantly smaller in the schizophrenia patients. Only the residual subtype showed a significant reduction in cerebral and hemispheric volumes than controls ($p<0.05$). The volumes of right and left ventricle, separately and together were larger than controls ($p<0.03$). The ventricle-to-brain ratios (VBRs) were greater in the cases ($p<0.05$). The paranoid subtype patients had larger ventricles and VBRs than controls ($p<0.05$). The lateral ventricle volumes and VBRs in the undifferentiated subtype were similar to the controls. In the residual subtypes, the ventricular volumes were similar to and the VBRs were larger than controls ($p<0.05$).

Conclusion: Schizophrenia is a heterogeneous disorder regarding its symptoms and neuropathological changes. The patterns of change in the cerebral and ventricular volumes differed in the studied 3 subtypes.

Keywords: Stereology, MRI, schizophrenia, cerebral hemisphere, lateral ventricle

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Introduction

Schizophrenia is the most common and the most severe psychotic disorder which presents with delusions, hallucinations, disorganized behavior and speech, and negative symptoms.[1] Despite its unknown etiology, both Kraepelin [2] and Bleuler,[3] who first described the disease, believed that eventually a relationship between the structural brain abnormalities and the etiology of schizophrenia would be revealed. In the late nineteenth and early twentieth centuries, lots of autopsies were performed to seek the anatomical abnormalities of the brain in schizophrenic patients, but many of them failed primarily due to low precision of measuring techniques and instruments, and the fact that the scientists expected overt abnormalities.[4-6] Later, controlled trials were negative for brain abnormalities in schizophrenia.[7,8] Following the first report on presence of abnormal findings on brain CT scan of schizophrenic patients by Johnstone et al,[9] the enthusiasm about the subject resurged. The autopsy studies were started again by Kovelman and Scheibel [10] and soon it was widely agreed that schizophrenia must be considered as an organic brain disorder.[11]

With the first MR study in schizophrenia by Smith et al in 1984, [12] the researchers were offered a unique opportunity to examine the special brain areas in alive patients. Unlike CT scan, MR images can discriminate between the grey and white matter of brain with a much better resolution, so that MRI has become the imaging modality of choice in evaluation of brain changes during schizophrenia. [13]

Although some MR studies have reported changes in brain volume [14-25] and the volume of lateral ventricles [14-16, 20, 22, 24, 26-33], there are some reports that could not find any meaningful difference in the size of brain[29-32] and lateral ventricles[34,35] between normal controls and the patients with schizophrenia. The discrepancy can be partly due to the heterogenicity of schizophrenia subtypes,[36] as well as differences in calculating the cerebral size using the MR slices. [37] Moreover, some studies suggest that brain morphology can predict the course of the disease and the outcome for neuroleptic drugs use.[38]

In the present study, schizophrenia was regarded as a heterogeneous disorder, and the changes in cerebral hemispheres and lateral ventricles volumes in 3 subtypes of schizophrenia (paranoid, undifferentiated, and residual) were compared with the normal controls. The calculations for measuring cerebral hemispheres and lateral ventricles volumes by means of MR images have been done by unbiased stereological methods.[37]

Materials and Methods

Patients

Twenty-nine patients with schizophrenia (21 men and 8 women) were selected from the patients who referred to the day clinic or were hospitalized in Iran and Razi Psychiatry Hospitals, Tehran. The patients were vigilantly interviewed by 2 expert psychiatrists; and after confirming a diagnosis of schizophrenia, the patients were grouped as paranoid, undifferentiated or residual subtypes according to the diagnostic criteria of DMS-IV.[1] The patients with neurological diseases such as epilepsy and mental retardation, illicit drug users, and those with a history of head trauma were excluded. All the studied patients were receiving neuroleptic medication. Of 29 schizophrenic patients, 10 were paranoid type (7 men, 3 women); 10 undifferentiated (7 men, 3 women) and 9 residual (5 men, 4 women.)

To match the controls and cases for age and gender, for each patient a healthy volunteer of the same gender and of the similar age range (± 5 years) was chosen that was negative for neurological diseases, illicit drug use and history of head trauma, and their psychiatric well-being was approved by an expert psychiatrist.

MR imaging

All the cases and controls underwent brain MRI in Kourosh Imaging Center, Tehran. The MR system was a MAGNETOM Symphony Maestro Class, 1.5 T scanner (Siemens, Germany.) MR parameters were: 3-D MRI, complete coronal series, 1.5 mm slices without interslice gaps, TR= 1,920 ms, TE= 3.93 ms, TI= 1,100 ms, matrix size= 256 × 179, FOV= 240 × 240 mm, and a scanning time of 5 minutes and 40 seconds. The imaging data was saved on CD.

Calculations using stereological methods

The imaging data CD was retrieved using the software Osiris. The outline of the hemispheres and the lateral ventricles were carefully determined.(Figure 1) Then using a point grid, the surface area of each hemisphere and lateral ventricle was manually calculated in Photoshop®. (Figure 2) The volumes were calculated using Cavalieri's Principle, which is a stereological method,[37] by multiplying the sum of consecutive surface areas in coronal slices by their thicknesses. Stereological methods are the best unbiased methods available for 3-D calculations from 2-D images. [37] For statistical analysis, we used the ventricle-to-brain ratio (VBR), as well as the volumes of hemispheres and lateral ventricles.

Statistical Analysis

The means, variances, and standard deviations of the parameters were calculated and then, one-tailed Student's t-test was used to compare the demographic characteristics and cerebral and ventricular volumes between the cases and controls.

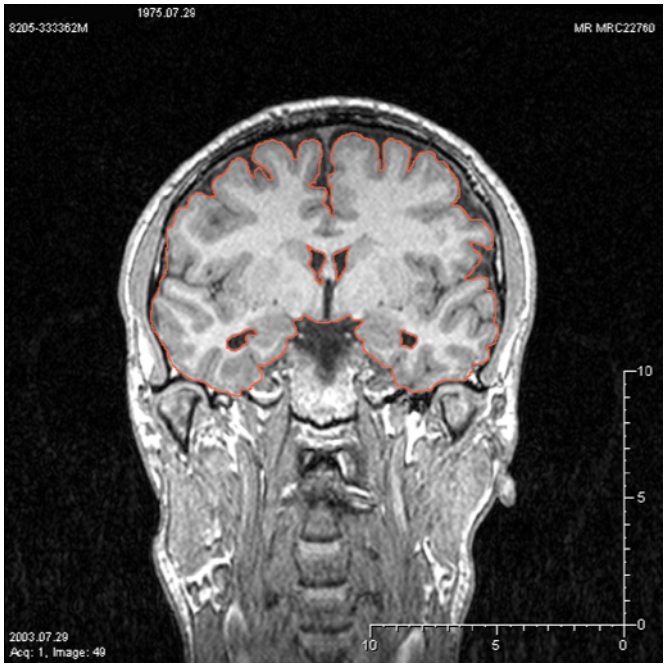

Figure 1: Determining the outline of hemispheres and lateral ventricles

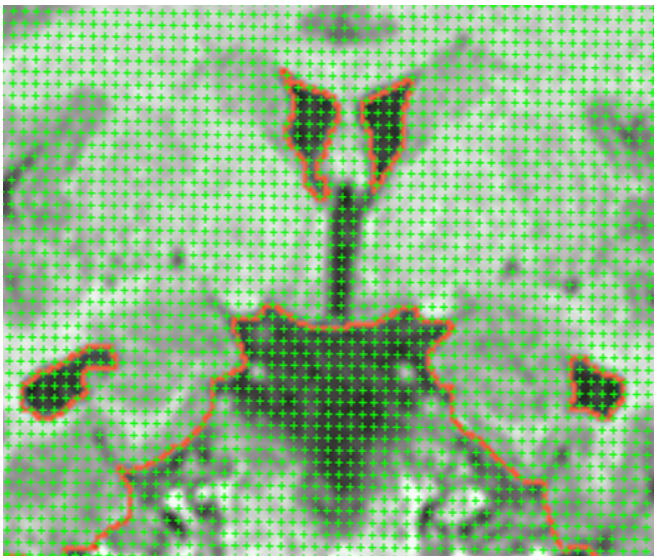

Figure 2: Calculation of the surface area of lateral ventricles using point counting of a point grid

To compare the demographic data and cerebral and ventricular volumes among the three schizophrenic subtypes, the one way ANOVA; and for paired comparisons among the subtypes, Tukey's procedure was used. A p value of less than 0.05 was considered statistically significant. The correlation coefficient was determined by Pearson and Spearman's tests. All the calculations were done using SPSS 10.

Results

Table 1 presents the demographic data and cerebral and ventricular volumes in the schizophrenia patients (and the subtypes) and healthy controls. Tables 2-4 present these data between different subtypes (paranoid, undifferentiated, and residual) with their controls. The mean duration of schizophrenia was 11.3± 8.4 years (6 months to 36 years). Since the disease duration did not have a normal distribution pattern in our patients, we adopted Spearman's test to assess the relationship between the brain volumes and disease duration. So, we found that the cerebral volume (p= 0.017), right hemisphere volume (p= 0.006) and left hemisphere volume (p= 0.008) reduced with the longer disease durations, but the disease duration appeared to have no effect on lateral ventricular volumes.

Table 1: Comparison of demographic characteristics and volumetric information between schizophrenic patients and normal controls

	Schizophrenics (N=29)	Normal controls (N=29)	Percentile difference(%)	P value
Age (years)	36.41±12.74	36.52±12.66	-0.30	NS
Weight (kg)	67.59±9.55	72.69±9.91	-7.01	NS
Sex (M/F)	21/8	21/8	-	-
Handedness (R/L)	27/2	23/6	-	-
WBV (cm^3)	1262.64±145.51	1318.01±144.46	-4.20	NS
RHV (cm^3)	549.47±68.26	572.16±65.84	-3.97	NS
LHV (cm^3)	545.37±66.97	569.73±64.74	-4.28	NS
WLvV (mm^3)	19433.75±6599.91	15078±6488.26	28.89	0.01
RLvV (mm^3)	8880.09±3476.82	6903.81±2568.85	28.63	0.02
LLvV (mm^3)	10553.66±3571.17	8174.82±4113.35	29.10	0.02
VBR (W)	$1.55\times10^{-2}\pm5.35\times10^{-3}$	$1.13\times10^{-2}\pm3.91\times10^{-3}$	37.60	0.001
VBR (R)	$1.63\times10^{-2}\pm6.20\times10^{-3}$	$1.19\times10^{-2}\pm3.60\times10^{-3}$	36.44	0.002
VBR (L)	$1.95\times10^{-2}\pm6.81\times10^{-3}$	$1.41\times10^{-2}\pm5.77\times10^{-3}$	38.81	0.002

Raw mean±SD, M=Male, F=Female, R=Right-handed, L=Left-handed, WBV= Whole brain volume, RHV=Right hemisphere volume, LHV=Left hemisphere volume, WLvV= Whole lateral ventricle volume, RLvV=Right lateral ventricle volume, LLvV=Left lateral ventricle volume, VBR(W)=WLvV/WBV, VBR(R)=RLvV/RHV, VBR(L)=LLvV/LHV, NS=Non significant

Table 2: Comparison of demographic characteristics and volumetric information between paranoid subtype of schizophrenic patients and normal controls

	Paranoid (N=10)	Normal controls (N=10)	Percentile	P value
Age (years)	33.70±15.47	34±14.85	-0.88	NS
Weight (kg)	70.80±10.58	66.90±10.84	5.83	NS
Sex (M/F)	7/3	7/3	-	-
Handedness (R/L)	7/3	9/1	-	-
WBV (cm^3)	1328.29±171.31	1310.74±166.19	1.34	NS
RHV (cm^3)	581.56±78.12	575.02±79.35	1.14	NS
LHV (cm^3)	574.78±81.09	566.76±71.14	1.42	NS
WLvV (mm^3)	22075.78±6868.13	14681.92±6273.19	50.36	0.02
RLvV (mm^3)	9892.52±3587.25	6443.16±2642.60	53.54	0.03
LLvV (mm^3)	12183.26±4051.13	8238.76±3853.80	47.88	0.04
VBR (W)	$1.69\times10^{-2}\pm6.08\times10^{-3}$	$1.11\times10^{-2}\pm4.05\times10^{-3}$	52.71	0.02
VBR (R)	$1.73\times10^{-2}\pm6.92\times10^{-3}$	$1.11\times10^{-2}\pm4.13\times10^{-3}$	55.57	0.03
VBR (L)	$1.16\times10^{-2}\pm8.15\times10^{-3}$	$1.43\times10^{-2}\pm5.53\times10^{-3}$	-18.67	0.03

Raw mean±SD, M=Male, F=Female, R=Right-handed, L=Left-handed, WBV= Whole brain volume, RHV=Right hemisphere volume, LHV=Left hemisphere volume, WLvV= Whole lateral ventricle volume, RLvV=Right lateral ventricle volume, LLvV=Left lateral ventricle volume, VBR(W)=WLvV/WBV, VBR(R)=RLvV/RHV, VBR(L)=LLvV/LHV, NS=Non significant

Table 3: Comparison of demographic characteristics and volumetric information between undifferentiated subtype of schizophrenic patients and normal controls

	Undifferentiated (N=10)	Normal controls (N=10)	Percentile difference(%)	P value
Age (years)	33.60±10.57	34.90±11.69	-3.72	NS
Weight (kg)	64.90±9.53	71.40±9.48	-9.10	NS
Sex (M/F)	7/3	7/3	-	-
Handedness (R/L)	10/0	9/1	-	-
WBV (cm^3)	1304.45±101.65	1360.09±116.57	-4.09	NS
RHV (cm^3)	571.43±47.53	589.40±48.12	-3.50	NS
LHV (cm^3)	565.42±42.45	592.04±51.19	-4.50	NS
WLvV (mm^3)	18616.31±7136.19	17174.99±8235.16	8.39	NS
RLvV (mm^3)	8880.51±4166.60	7955.99±2835.93	11.62	NS
LLvV (mm^3)	9735.80±3256.45	9218.99±5513.61	5.61	NS
VBR (W)	$1.42\times10^{-2}\pm4.97\times10^{-3}$	$1.24\times10^{-2}\pm4.84\times10^{-3}$	14.98	NS
VBR (R)	$1.55\times10^{-2}\pm6.81\times10^{-3}$	$1.33\times10^{-2}\pm3.76\times10^{-3}$	16.38	NS
VBR (L)	$1.72\times10^{-2}\pm5.42\times10^{-3}$	$1.51\times10^{-2}\pm7.69\times10^{-3}$	13.80	NS

Raw mean±SD, M=Male, F=Female, R=Right-handed, L=Left-handed, WBV= Whole brain volume, RHV=Right hemisphere volume, LHV=Left hemisphere volume, WLvV= Whole lateral ventricle volume, RLvV=Right lateral ventricle volume, LLvV=Left lateral ventricle volume, VBR(W)=WLvV/WBV, VBR(R)=RLvV/RHV, VBR(L)=LLvV/LHV, NS=Non significant

Table 4: Comparison of demographic characteristics and volumetric information between residual subtype of schizophrenic patients and normal controls

	Residual (N=9)	Normal controls (N=9)	Percentile difference(%)	P value
Age (years)	42.56±10.57	41.11±11.14	3.53	NS
Weight (kg)	71.33±7.68	76.22±9.80	-6.42	NS
Sex (M/F)	5/4	5/4	-	-
Handedness (R/L)	7/2	8/1	-	-
WBV (cm^3)	1143.23±76.52	1279.34±150.7284	-10.64	0.02
RHV (cm^3)	489.42±30.89	549.82±67.39	-10.99	0.02
LHV (cm^3)	490.40±35.87	548.24±69.83	-10.55	0.04
WLvV (mm^3)	17406.41±5283.23	13190.14±4131.82	31.97	NS
RLvV (mm^3)	7754.69±2365.43	6246.55±2014.29	24.14	NS
LLvV (mm^3)	9651.71±3028.61	6943.59±2288.45	39	NS
VBR (W)	$1.53\times10^{-2}\pm5.11\times10^{-3}$	$1.02\times10^{-2}\pm2.46\times10^{-3}$	49.66	0.02
VBR (R)	$1.59\times10^{-2}\pm5.12\times10^{-3}$	$1.12\times10^{-2}\pm2.57\times10^{-3}$	41.71	0.03
VBR (L)	$1.98\times10^{-2}\pm6.51\times10^{-3}$	$1.26\times10^{-2}\pm3.43\times10^{-3}$	56.50	0.01

Raw mean±SD, M=Male, F=Female, R=Right-handed, L=Left-handed, WBV= Whole brain volume, RHV=Right hemisphere volume, LHV=Left hemisphere volume, WLvV= Whole lateral ventricle volume, RLvV=Right lateral ventricle volume, LLvV=Left lateral ventricle volume, VBR(W)=WLvV/WBV, VBR(R)=RLvV/RHV, VBR(L)=LLvV/LHV, NS=Non significant

Also, the VBRs did not significantly correlate with the disease duration. Disease duration was longer in the residual subtype than in the paranoid (p= 0.04,) but in the undifferentiated subtype it was not different from the residual and paranoid subtypes.

Pearson's test did not reveal any significant correlation between the patients' and controls' ages with their cerebral or the right and left hemispheric volumes.

Cerebral volumes were smaller in the residual subtype than the other two. Cerebral volume and the right and left hemispheric volumes in the residual subtype were respectively 13.93% (p=0.01), 15.82% (p=0.004), and 14.68% (p=0.01) less than the values in the paranoid subtype; and 12.36% (p=0.02), 14.35% (p=0.01), and 13.27% (p=0.02) less than the same values in the undifferentiated subtype. The lateral ventricular volumes were not significantly different among the 3 groups.

As the controls were matched with the patients, we could perform a conditional logistic regression analysis. The results showed that only the increase in the lateral ventricular volumes (p=0.03) and increased ratio of the total volumes of the lateral ventricles to the cerebral volume (p=0.005) were predictive in the diagnosis of schizophrenia. In the paranoid subtype, only the increased volume of the right ventricle (p=0.04) served as the predictive model. In the residual subtype, only after transforming the outcome variable to a logarithmic transformation, the increase in the ratio of the total lateral ventricular volumes to the cerebral volume could serve as a predictive model for the diagnosis of this subtype. The analysis could not yield a predictive model for the undifferentiated subtype.

Discussion

For 200 years now, the studies by Pinel [39] and Kertschmer [40] have drawn the scientists' attention to the role of cerebral volume in mental illnesses. Some experts believe that the smaller cerebral volumes in mental diseases result from perinatal complications, neurodevelopemental disorders or both.[41-44] Evaluating the volumes of different structures in the brain, it is necessary to determine the total cerebral volume so that we can say if the change in the volume of those

structures is secondary to overall changes in the cerebral volume or has occurred independently.

In the present study, despite the smaller cerebral and hemispheric volumes in the schizophrenic patients than controls, the difference was not of significance. Among 3 schizophrenia subtypes, only the residual subtype had significantly smaller cerebral and hemispheric volumes than the controls ($p<0.05$).

Although some researchers did not detect any significant difference between the cerebral and hemispheric volumes of the schizophrenic patients and the healthy individuals [29-32], some others believe that in schizophrenia the brain is smaller than normal.[14-25] Ward et al [44] noticed a subtle yet significant decrease in the cerebral volume of the patients with schizophrenia as compared to normal.

The present study did not find smaller cerebral volumes with schizophrenia. However, the patients in the residual subtype had smaller brains than their normal controls. Therefore, we can attribute the controversies about the changes in the cerebral volume during schizophrenia partly to heterogenicity of the disease. In other words, when the study population consists more of the residual subtype, the changes in cerebral volumes would be more significant, otherwise no difference may be found.

The changes in the cerebral volumes of the residual subtype can be explained in 2 ways: first, the disease duration was longer in the residual subtype and as stated earlier in the results, the disease duration had a negative correlation with the right and left hemispheres volumes ($p< 0.05$). This explanation emphasized the effect of disease chronicity on brain shrinkage. However, this argument is controversial. Some studies have reported presence of structural brain abnormalities in the first-episode schizophrenia.[46] Hence, they reject the role of disease chronicity in brain changes and mainly support the neurodevelopemental bases for brain abnormalities, and believe that the brain changes are rather 'static' after the disease has commenced. [46, 47] On the other hand, the longitudinal studies on the brain structural changes over years believe that the changes are of a 'progressive' nature in schizophrenia.[48, 49] They suggest that disease chronicity, the progressive nature of schizophrenia and the heterogenicity of the subtypes may play a role in the structural brain changes.[47]

The second explanation for smaller cerebral volumes in residual subtype than the controls can be attributed to the higher prevalence of the negative symptoms and lack of positive symptoms in this subtype. Some other research has shown a direct relationship between the negative schizophrenic symptoms (and lack of positive symptoms) with structural changes in the brain.[14,16,45]

In the present study, the volumes of right and left lateral ventricles (separately and together) were higher than the normal controls ($p<0.03$). VBRs were also higher in these patients ($p<0.003$).

Schizophrenia subtypes differed regarding the changes in the brain volumes:

In the paranoid subtype, lateral ventricles were larger than their controls, therefore their VBRs were larger as well ($p<0.05$). In the undifferentiated subtype, none of the parameters differed from the normal controls. In the residual subtype, although the ventricular volumes were similar to those of the controls, the smaller cerebral and hemispheric volumes in the patients resulted in larger VBRs than the controls ($p<0.05$).

Although larger-than-normal lateral ventricles are the commonest finding in the schizophrenia, [13, 50] it is not specific and can be found in a number of other disorders such as Alzheimer's disease, hydrocephalus, and Huntington's chorea. In general, enlarged lateral ventricles are interesting findings which can indicate paraventricular neuronal tissue loss or embryonic dysgenesis.[13]

The current study supports the finding of enlarged lateral ventricle in schizophrenia, but not as a constant finding with all the subtypes. The ventricular enlargement was only observed in the paranoid subtype. The VBRs were larger than normal in the residual subtype for their smaller brains, and in the paranoid subtype for their larger ventricles, but did not change in the undifferentiated subtype. As indicated earlier, enlarged ventricles unlike smaller brain volume were not related to the disease chronicity.

According to the findings of the present study, it can be stated that only enlargement of the lateral ventricles and increased ventricular-to-cerebral volume ratio (VBR) can be used as a predictive model in the diagnosis of schizophrenia. We observed that there are 3 different patterns of brain structural changes in the 3 subtypes of paranoid, undifferentiated and residual schizophrenia. In the paranoid subtype, the enlarged right ventricle was diagnostically predictive. In the patients with undifferentiated schizophrenia, cerebral and ventricular volumes and VBRs were similar to the controls. In the residual subtype, increased ventricular-to-cerebral volume ratio(VBR) could serve as a predictive model for diagnosis of this subtype. The patients with residual schizophrenia have smaller brains than normal but normal lateral ventricles, so that their VBRs are larger than normal. Some experts believe that the residual subtype of schizophrenia is not an independent type, and in fact it is the result of chronicity of other subtypes, so it cannot be concluded that the smaller brain size in this subtype is due to the longer

disease duration or these patients have this abnormality per se.

Our results show that schizophrenia is a heterogeneous disorder both in the symptoms and the structural changes of the brain.

Schizophrenia is still a clinical diagnosis, based on the criteria in DMS-IV or ICD-10. It is probable that the patients with different neuropathologies present different symptoms of the disease. Thus, some experts consider at least 3 different syndromes with different neuropathologies: paranoid, disorganized, and negative.[51] DMS-IV classification of the patients under subtypes of paranoid, disorganized, undifferentiated, catatonic, and residual shows the heterogenicity of schizophrenia. However, unfortunately most of the studies have put all their schizophrenia patients in one group rather than in different subtypes.

The present study tried to regard the patients in different subtypes, but we could not find an adequate number of patients in subtypes of disorganized and catatonic schizophrenia. We hope that further studies on those missing subtypes will help with a new classification of schizophrenia on the basis of brain structural changes which are more reliable than the current clinical criteria.

Further research on the first-episode schizophrenia along with longitudinal studies will help to decide if the brain changes in schizophrenia are static or progressive, and if the progression can be overcome by appropriate treatment. Some researcher state that the similar cerebral changes could be found in the first degree asymptomatic relatives of the schizophrenia patients [47] and the structural changes could be used as a genetic maker for both identifying the high-risk family members and in preventive studies. [39] More comprehensive studies on the first degree relatives of those patients are recommended.

Acknowledgment

The authors wish to thank the managers, physicians and staff of the Iran and Razi Psychiatry Hospitals (Tehran). Our special thanks go to Dr Mehrdad Eftekhar and Dr. Zia Ghaem Magham Farahani for the assistance in patient selection. We are grateful to Dr Dariush Etemadi, the CEO of Koroush Imaging Centre (Tehran) and the radiology staff for imaging the patients and healthy volunteers of this study.

This study was granted by the Deputy for Research, Mashad University of Medical Sciences.

References

1. Sadock BJ, Sadock VA. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 7th ed. Philadelphia: Lippincott Williams and wilkins, 2000: 1097-1105.
2. Kraepelin E. Dementia Praecox. New York, Churchill Livingstone Inc., 1919.
3. Bleuler E. Dementia Pracox oder ruppe der Schizophrenien. Leipzig: F. Denticke, 1911.
4. Alzheimer A. Beitrage zur pathologischen Anatomie der Hirnride und zur anatomischen Grundlage einiger Psychosen. Monatsschrift fÜr Psychiatrie und Neurologic 1897; 2: 82-120.
5. Southard EE. A study of the dementia praecox group in the light of certain cases showing anomalies or scleroses in particular brain regions. Am J Insanity 1910; 67: 119-176.
6. Southard EE. On the topographic distribution of cortex lesions and anomalies in dementia praecox with some account of their functional significance. Am J Insanity 1915; 71: 603-671.
7. Dunlap C. Dementia praecox: Some preliminary observations on brains from carefully selected cases, and a consideration of certain sources of error. Am J Psychiatry 1924; 80: 403-421.
8. Rowland L, Mettler F. Cell concentration and laminar thickness of frontal cortex of psychotic patients. J comp Neurol 1949; 90: 255.
9. Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L. Cerebral ventricular size and congnitive impairment in chronic schizophrenia. Lancet 1976; 2: 924-926.
10. Kovelman JA, Scheibel AB. A neurohistological correlate of schizophrenia. Biol Psychiatry 1984; 19: 1601-1621.
11. Henn FA, Nasrallah HA. Schizophrenia as a brain disease. New York, Oxford university press, 1982.
12. Smith RC, Calderon M, Ravichandran GK, Largen J, Vroulis G, Shvartsburd A, Gordon J, Schollar JC. Nuclear magnetic resonance in schizophrenia: a preliminary study. Psychiatry Res 1984; 12: 137-147.
13. Shenton ME, Dickey CC, Frunin M, McCarley RW. A review of MRI finding in schizophrenia. Schiz Res 2001; 49: 1-52.
14. Andreasen NC, Ehrhardt JC, Swayze VW 2nd, Alliger RJ, Yuh WT, Cohen G, Ziebell S. Magnetic resonance imaging of the brain in schizophrenia; The pathophysiologic significance of structural abnormalities. Arch Gen Psychiatry 1990; 47: 35-44.
15. Andreasen NC, Flashman L, Flauman L, Flaum M, Arndt S, Swayzer V 2nd, O'Leary DC, Ehrhardt JC, Yuh WT. Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. JAMA 1994; 272: 1763-1769.
16. Gur RE, Mozley PD, Shtasel DL, Cannon TD, Gallacher F, Turetsky B, Grossman R, Gur RC: Clinical sybtypes of schizophrenia: Differences in brain and CSF Volume. Am J Psychiatry 1994; 151: 343-350.
17. Gur RE, Cowell P, Turetsky BI, Gallacher F, Cannon T, Bilker W, Gur RC. A followup magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. Arch Gen Psyc hiatry 1998; 55: 145-152.
18. Gur RE, Turetsky BI, Bilker WB, Gur RC. Reduced gray matter volume in schizophrenia. Arch Gen Psychiatry 1999; 56: 905-911.
19. Jernigan TL, Zisook S, Heaton RK, Moranville JT, Hesselink JR, Bnaff DL. Magnetic resonance imaging abnormalities in lentricular nuclei and cerebral cortex in shchizophrenia. Arch Gen Psychiatry 1991; 48: 881-890.
20. Nasrallah HA, Schwarzkopf SB, Olson SC, Coffman JA. Gender differences in schizophrenia on MRI brain scans. Schiz Bull 1990; 16: 205-210.
21. Rajarethinam RP, DeQuardo JR, Nalepa R, Tandon R. Superior temporal gyrus in schizophrenia: a volumetric magnetic resonance imaging study. Schiz Res 2000; 41: 303-312.
22. Sanfilipo M, Lafargue T, Arena L, Rusinek H, Kushner K, Lautin A, Lorenagna C, Vaid G, Rotrosen J, Wolkin A. Fine volumetric analysis of the cerebral ventricular system in schizophrenia: further evidence for multifocal mild to moderate enlargement. Schiz Bull 2000; 26: 201-216.
23. Staal WG, Hulshoff Pol HE, Schnack H, Van der Schot AC, Kahn RS. Partial volume decrease of the thalamus in relatives of patients with schizophrenia. Am J Psychiatry 1998; 155: 1784-1786.

24. Whitworth AB, Honeder M, Kremser C, Kemmler G, Felber S, Hausmann A, Wanko C, Wechdorn H, Aichner F,Stuppaeck CH, Fleischhacker WW. Hippocampal Volume reduction in male schizophrenic patients. Schiz Res 1998; 31: 73-81.
25. Ward KE, Fridman L, Wise A, Schulz SC: Do schizophrenics have small heads and / or brains? A Meta – analysis. Schiz Res 1995; 15: 32.
26. Barr WB, Ashtari M, Bilder RM, Degreef G, Lieberman JA: Brain morphometric comparison of first episode schizophrenia and temporal lobe epilepsy. Br J Psychiatry 1997; 170: 515-519.
27. Buchsbaum MS, Yang S, Hazlett E, Siegel BV, Germans M, Haznedar M, O'Flaithbheartagih S, Wei T, Silverman J, Siever LJ. Ventricular Volume and asymmetry in schizotypal personality disorder and schizophrenia assessed with magnetic resonance imaging. Schiz Res 1997; 27: 45-53.
28. Degreef G, Ashtari M, Bogerts B, bilder RM, Jody PN, Alvir JM, Lieberman JA: Volumes of ventricular systems subdivisions measured from magnetic resonance images in first episode schizophrenic patients. Arch Gen Psychiatry 1992; 49: 531-537.
29. Delisi LE, Stritzke P, Riordan H, Holan V, Boccio A, Kushner M, McClelland J, Van Eyl O, Anand A: The timing of brain morphological changes in schizophrenia and their relationship to clinical outcome. Biol Psychiatry 1992; 31: 241-254.
30. Flaum M, Swayze II VW, O'Leary DS, Yuh WT, Ehrhardt JC, Arndt SV, Andreasen NC: Effects of diagnosis, laterality, and gender on brain morphology in schizophrenia. Am J Psychiatry 1995; 152: 704-714.
31. Klose Jr JR, Cadet JL, Pickar D, Weinberger DR. Quantitative neuroanatomy in schizophrenia. A controlled magnetic resonance imaging study. Arch Gen Psychiatry 1988; 45: 533-541.
32. Nopoulos P, Torres I, Flaum M, Andreasen NC, Ehrhardt JC, Yuh WT. Brain morphology in first-episode schizophrenia. Am J Psychiatry 1995; 152: 1721-1723.
33. Symonds LL, Archibald SL, Grant I, Zisook S, Jernigan TL. Does an increase in sulcal or ventricular fluid predict where brain tissue is lost? J Neuroimaging 1999; 9: 201-209.
34. Rossi A, Stratta P, D'Albenzio L, Tartaro A, Schiazza G, di Michele V, Bolino F, Casacchia M: Reduced temporal lobe areas in schizophrenia: preliminary evidences from a controlled multiplanar magnetic resonance imaging study. Biol Psychiatry 1990; 27: 61-68.
35. Shenton ME, Kikinis R, McCarley RW, Metcalf D, Tieman J, Jolesz FA. Application of automated MRI volumetric measurement techniques to the ventricular system in schizophrenics and normal controls. Schiz Res 1991; 5: 103-713.
36. Hayashi T, Hotta N, Andoh T, Mori M, Fukatsu N, Suga H. Magnetic resonance imaging finding in schizophrenia and atypical psychoses. J Neural transm 2001; 108: 695-709.
37. Sheline YI, Black KJ, Lin DY, Christensen GE, Gado MH, Brunsden BS, Vannier MW. Stereological MRI Volumetry of the frontal lobe. Psychiatry Res 1996; 67: 203-214.
38. Vita A. Structural brain imaging: relationship to treatment resoponse and clinical outcome of schizophrenia. Eur Neuropsychopharmacol 1997; 7: 130-131.
39. Pinel P. Traite medico philosophique sur l'alienation mentale boulamania. Paris, Richard Caille et Ravier, 1801.
40. Kretschmer E. Physique and Character. New York, Harcourt Brace Jovanovich Publishers, 1925.
41. Andreasen N, Nasrallah HA, Dunn V, Olson SC, Grove WM, Ehrhardt JC, Coffman JA, Crossett JH. Structural abnormalities in the frontal system in schizophrenia. A magnetic resonance imaging study. Arch Gen Pychiatry 1986; 43: 136-144.
42. Pearlson GD, Barta PA, Schrami FV. Brain size in schizophrenia [Letter]. Arch Gen Psychiatry 1991; 48: 181-182.
43. Zipursky RB, Lim KO, Pfefferbaum A. Brain size in Schizophrenia. Arch Gen Psychiatry 1991; 48: 179-180.
44. Ward KE, Friedman L, Wise A, Schulz SC. Meta – analysis of brain and cranial size in schizophrenia. Schiz Res 1996; 22: 197-213.
45. Sanfilipo M, Lafargue T, Rusinek H, Arena L, Lautin A, Feiner D, Rotrosen J, Wolkin A. Volumetric measures of the frontal and temporal lobe regions in schizophrenia: relationship to negative symptoms. Arch Gen Pscyhiatry 2000; 57: 471-480.
46. Nopoulos P, Torres I, Flaum M, Andreasen NC, Ehrhardt JC, Yuh WT. Brain morphology in first – episode schizophrenia. Am J Psychiatry 1995; 152: 1721-1723.
47. Gelder MG, Lopez – Ibor JJ, Andreasen N. New Oxford Textbook of Psychiatry. Oxford: Oxford University Press, 2000: 607-609.
48. Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study in schizophrenia. Arch Gen Psychiatry 2003; 60: 585-594.
49. Cahn W, Pol HE, Lems EB, Van Haren NE, Sehnack HG, Van der Linden JA, Schothorst PF, Van Engeland H, Kahn RS. Brain Volume changes in first – episode schizophrenia: a 1-year follow- up study. Arch Gen Psychiatry 2002; 59: 1002-1010.
50. Shelton RC, Weinberger DR: X-ray computerized tomography studies in schizophrenia: a review and synthesis. In: Nasrallah HA, Weinberger DR (Eds.). Handbook of Schizophrenia: The Neuropathology of Schizophrenia. Vol. I. New York: Elsevier Science Publishers, 1986: 207-225.
51. Gelder M, Cath D, Mayou R, Cowen PH. Oxford Textbook of Psychiatry, 3rd ed. Oxford : Oxford University Press, 1996: 246-294.