Computarised brain tomography in patients with Schizophrenia.

Dexy Prieto-Rincón[1], María Angela Montiel, Ernesto Bonilla, Lorena Piñerúa, Eduardo Mora and Silvia Siciliano.

Instituto de Investigaciones Biomédicas (Inbiomed) – Fundacite Zulia. P.O. Box 121. Maracaibo, Venezuela.

Key words: Schizophrenia, lateral ventricles, Sylvian fissure, brain tomograpny.

Abstract. We carried out brain tomography of 27 patients with schizophrenia and 17 normal control subjects. DSM-IV criteria were used for diagnosis. The parameters studied were: brain volume, lateral and third ventricles, brain surface and brain indexes. Previously the patients were evaluated with the following clinical scales: Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), Global Assessment of Functioning Scale (GAF) and the GRAFFAR scale to evaluate cultural and socioeconomical levels. We detected an increase in the right and left lateral ventricles: brain ratios, an increase in the width of Sylvian fissures and in the third ventricle index. We did not find differences that could be related to sex or to a familial history of mental disease. No differences were observed in the group receiving medication when compared witn the group of untreated patients.

Tomografía cerebral computarizada en pacientes con esquizofrenia.

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Palabras clave: Esquizofrenia, ventrículos laterales, cisura de Silvio, tomografía cerebral.

Resumen. Se practicó la tomografia cerebral en 27 pacientes con esquizofrenia y 17 sujetos controles normales. Los criterios del DSM-IV se utilizaron para el diagnóstico. Los parámetros usados fueron los siguientes: volumen cerebral, ventrículos laterales y tercer ventriculo, superficie cerebral y los índices cerebrales. Los pacientes fueron evaluados previamente con las siguientes escalas clinicas: Escala de los Síntomas Positivos y Negativos (PANSS), la Escala Breve de Evaluación Psiquiátrica (BPRS), la Escala

de Funcionamiento Global (GAF) y la Escala de GRAFFAR para evaluar los niveles culturales y socioeconómicos. Se detectó un incremento en el cociente entre el tamaño de los ventrículos laterales derecho e izquierdo y el cerebro, un aumento en la anchura de las cisuras de Sylvio y en el índice del tercer ventrículo. No se encontraron diferencias que pudieran relacionarse con el sexo o con la historia familiar de enfermedad mental. Tampoco se observaron diferencias entre el grupo que recibió medicación y el grupo de pacientes no tratados.

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INTRODUCTION

Schizophrenia affects 1% of the world population and it is considered the most deleterious mental disease in the young adult. It has been described as a developmental disorder in which the primary neuropathological abnormalities occur during brain development long before the disease is clinically manifested (1, 2).

The first computerised tomography (CT) scan study in schizophrenia was carrried out by Johnstone *et al* (3) who reported that a sample of 13 chronically hospitalised patients with schizophrenia had significantly larger lateral ventricles than eight normal volunteers; in some cases the enlargement was considerable. The patients in this study were relatively old, with a chronic evolution and some of them had been subjected to lobotomy.

The enlargement of the third and lateral ventricles is one of the most frequently replicated neurobiological finding in schizopkenia (4, 5). In fact, a review of computerised tomography, magnetic resonance imaging (MRI), *post-mortem* and functional imaging studies found that the only well-established structural abnormality in schizophrenia is lateral ventricular enlargement (6). It has been established that it is not due to the effect of medication since it has also been detected in young nonmedicated patients (7, 8). According to some authors (9) although there is a difference in ventricular: brain ratio (VBR) between schizophrenic patients and controls which would seem to be an indisputable characteristic of schizophrenia the difference is smaller than has previously been thought, so that, although of undoubted theoretical interest in accounting for the aetiology of schizophrenia, it is probably too small to be of practical significance in diagnosis, or in differentiation of subtypes.

Ventricular enlargement is probably an ongoing process throughout the course of schizophrenic illness. Although some longitudinal studies have not provided definitive information with respect to this problem (10, 11) a prospective follow-up study of first episode cases of schizophrenic illness revealed that left cerebral ventricles

had significantly greater enlargement over time suggesting that a subtle active brain process may be continuing through the first few years of a schizophrenic illness causing greater than the normal adult cortical deterioration (12). Magnetic resonance brain imaging and neurobehavioral studies conducted at baseline and after 30 months in 40 patients with schizophrenia and 17 healthy controls revealed that both first-episode and previously treated patients had smaller brains and frontal and temporal lobes than controls at intake.

Longitudinally, reduction in frontal lobe volume was found only in patients whereas temporal lobe reduction was associated with decline in some neurobehavioral functions. The existence of neuroanatomical and neurobehavioral abnormalities in patients with first-episode schizophrenia indicates that the brain dysfunction occurred before clinical presentations although there is also evidence of progression in which anatomical changes may affect some clinical and neurobehavioral features of the illness (13).

We have performed a study comprising CT scannings of schizophrenic patients admitted to the Psychiatric Hospital in Maracaibo, Venezuela, in order to further investigate the relationship between brain volume, ventricular size and other parameters with the clinical characteristics of these patients.

MATERIALS AND METHODS

Materials

All brain CT scans were done with a Picker Synerview 66S/1200 SX scanner with displacement of -1000 to + 4000. Twelve slices (0.8 mm thick) were taken through the brain parallel to and starting 1cm above the orbitomeatal plane. The scanner was calibrated before every scanning.

Patients

Twenty seven subjects (18 men, 9 women; mean age ± SD, 31.3 ± 8.4) admitted to the Psychiatric Hospital of Maracaibo, Venezuela, met DSM-IV criteria (American Psychiatric Association, 1994) for schizophrenia. The control group comprised 17 normal members of the general population (9 men, 8 women; mean age ± SD, 31.2 ± 9.6) including medical students, and hospital workers, who volunteered to undergo CT. There were no significant differences in mean age, weight, and height across the groups. Each individual gave informed consent to participate in the research protocol. Patients were examined in separate occasions by two psychiatrists. All patients were free of medical and neurological disease, history of cranial trauma, alcohol or drug abuse for at least 4 weeks, or history of major psychiatric disorder among first degree relatives. Pregnant women were excluded from the study. Fifteen patients were receiv-

ing neuroleptics. The remaining twelve were free of treatment for at least 15 days before the CT scanning. Fourteen patients belonged to the group aged between 20 and 29 years; 7 to the group aged between 30 and 39 years and 6 to the group aged between 40 and 49 years.

The following parameters were estimated:

1. Brain volume was calculated as follows: Volume = area in all measured slices x 0.8 (14). The uppermost and lowermost slices of the brain were discarded.

2. The widths of the fissura interhemispherica and the fissura Sylvii were measured manually.

3. The lateral ventricle: brain ratio (VBR) was calculated for each hemisphere and for the whole brain dividing the ventricle area previously described by the total brain area for each slice, multiplying the result by 100 (14).The third ventricle: brain ratio was calculated similarly. Measurements were performed by digitizing the films using computer-based image analysis software and displaying them on a computer monitor. The neuroradiologists were blinded to the diagnosis of the subjects under study. The lateral and third ventricle areas and brain area were determined for each hemisphere.

4. The frontal index was estimated as the greatest width of the frontal horns divided by the width of the brain at the same level, multiplying the result by 100. The caudal index was calculated as the greatest width of the frontal horns measured over the *nucleus caudatus* divided by the width of the brain at the same level, x 100; the third ventricle index was computed as the greatest width of the third ventricle divided by the width of tne brain at the same level, x 100: the plexus index was determined as the distance between the center of the calcified choroid plexus seen in the trigonum area divided by the width of the brain at the same level, x 100 (14).

Clinical evaluation

After determining the subtype of schizophrenia each patient was assessed globally by the following scales: a) Positive and Negative Syndrome Scale (PANSS) (15) which permits the direct observation of affective, psychomotor, cognitive, perceptual, attentive, integrative and interactive functions; b) the Brief Psychiatric Rating Scale (BPRS) (16) to evaluate the actual clinical condition of the patients; it is basically a quantitative scale; c) the Global Assessment of funtioning Scale (GAF) which refers to the present labour and psychosocial activity of the patient (17); d) the Graffar Scale to identify the different cultural and socioeconomical levels of the patients through the investigation of their families (18).

Information concerning the patients and controls is given in Tables I and II.

Statistical analysis

Pearson's correlation coefficient, analysis of variance (ANOVA) and

TABLE I
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF 27 PATIENTS WITH SCHIZOPHRENIA AND 17 NORMAL CONTROLS

Characteristics	Patients	Normal Controls
Mean age in years ± S.D.	31.26 ± 8.42	31.18 ± 9.58
Sex		
Male	18	9
Female	9	8
Marital Status		
Single	24	7
Married	3	8
Divorced	---	2
Weight in Kg: Mean ± S.D.	68.89 ± 14.2	71.91 ± 15.36
Height in meters: Mean ± S.D.	1.66 ± 0.08	1.67 ± 0.08

TABLE II
DESCRIPTIVE DATA OF 27 SCHIZOPHRENIC PATIENTS

Years of education: Mean ± S.D. (range)	7.30 ± 4.25 (0-13)
Age of onset (years): Mean ± S.D.	21.67 ± 6.03
Duration of illness (years): Mean ± S.D. (range)	9.91 ± 7.57 (0.5-29)
Family history of mental disease	22
Number of hospitalizations	
0-5	22
Electroconvulsive theraphy	8
Subtypes of shizophrenia	
Catatonic	1
Disorganized	1
Paranoid	23
Undifferentiated	2

Student's t test, at the 5% level of significance, were done to examine sex differences within each group, differences between the patients with schizophrenia and controls, and the relationship among brain CT measures between the groups, especially with relation to age.

RESULTS

The demographic characteristics of the groups of patients and controls were similar except with regard to the marital status since 24 patients with schizophrenia were unmarried ($p<0.5$) (Table I).

The mean age for the patients at their first episode of illness was 21.67 years (S.D. 6.03) and the mean duration of illness was 9.9 years (S.D. 7.6). A history of mental disease in their families was detected in 22 patients. Between 0 and 5 admissions to the hospital were found in 22 patients.

With regard to the subtype of schizophrenia, 23 cases under study were paranoid (Table II). Acording to PANSS, 10 patients belonged to the positive subtype and 12 to the negative subtype.When comparing each one of these subtypes with their tomographic results no differences were detected among them. Similarly no differences were found between medicated and unmedicated patients in any of the tomographic measurements.

The mean value obtained after applying BPRS was 43.89 (S.D. 6.03) for all the 27 patients with schizophrenia. No differences were detected between medicated and unmedicated patients.

For GAF we found a mean value of 30.74 (S.D. 6.88) due to the patients alterations in communication at work and with their families, changes in judgment, mood, and thought. No significant correlation was found between these alterations and the CT measurements. Similarly, the results obtained after applying the GRAFFAR scale were not correlated with the tomographic results.

Brain volumes were similar in patients with schizophrenia and controls. These results remained unaltered when corrected for age, sex, year of onset of illness and subtype of schizophrenia (Table III).

No significant correlation between ventricular enlargement and duration of illness was found.

A significant increase in right and left lateral-ventricle: brain ra-

TABLE III
COMPUTARISED TOMOGRAPHY MEASUREMENTS IN 27 PATIENTS WITH SCHIZOPHRENIA AND 17 NORMAL CONTROLS (MEAN ± S.D)

	Patients	Normal Controls
Brain volume: ml	1.007 ± 228.38	955.37 ± 283.37
Brain width: cm	12.96 ± 1.22	12.97 ± 0.81
Brain length: cm	15.77 ± 1.07	16.10 ± 0.66
Width of right fissure Sylvii: cm	0.37 ± 0.17*	0.25 ± 0.15
Width of left fissure Sylvii: cm	0.40 ± 0.18*	0.25 ± 0.15
Right lateral ventricle: brain ratio	4.38 ± 1.61*	2.73 ± 1.03
Left lateral ventricle: brain ratio	4.56 ± 1.11*	3.02 ± 1.22
Third ventricle: brain ratio using brain volume in the scans where third ventricle was identified	0.54 ± 0.27	0.44 ± 0.18
Frontal index	32.30 ± 2.94	30.48 ± 5.16
Caudal index	12.69 ± 2.70	11.70 ± 2.98
Third ventricle index	5.69 ± 7.84*	2.38 ± 1.10
Plexus index	41.28 ± 4.89	39.83 ± 4.74

* $P<0.05$ when compared to controls.

tios were detected in the patients with schizophrenia when compared with the healthy volunteers ($p<0.05$) (Table III). This effect was found in both sexes and in the group of patients aged between 20 and 29 years ($F= 11.9$, $P= 0.008$ for the right and $F= 4.08$, $P= 0.001$ for the left) but not in the remaining age groups.

The patient group had significantly wider left and right fissuras Sylvii than the control group ($p<0.05$) (Table III). When corrected for sex and age this difference was found only in women ($p<0.05$) and in the group of 20 to 29 years of age ($F= 22.1$, $P= 0.01$ for right and $F= 16.3$, $P= 0.006$ for left fissuras Sylvii) but not in the remaining groups of patients with schizophrenia.

The third ventricle index was also larger in patients than in controls ($p<0.05$). No differences were observed with regard to frontal ($P= 0.60$), caudal ($P = 0.49$) and plexus indexes ($P= 0.38$). However, when corrected for sex the caudal index was significantly larger in women with schizophrenia ($p<0.05$). On the other hand this index was found to be increased in patients whose illness began before 30 years of age ($F= 6.79$, $P= 0.01$).

The third ventricle index when corrected for age did not vary in the group of patients aged 30 to 39 years ($F= 1.68$, $P= 0.13$) but remained significantly larger in the patients aged 20 to 29 ($F= 16.2$, $P=0.004$) and 40 to 49 years ($F=1.06$, $P = 0.01$).

In patients whose age of onset was 30 years or more the frontal index was larger than in patients whose disease began earlier ($p<0.05$).

The frontal and third ventricle indexes were significantly larger in individuals with paranoid schizophrenia than in other subtypes of schizophrenia ($p<0.05$).

DISCUSSION

The present study is in conformity with others previously reported (19, 20) with regard to the increase in volume of lateral ventricles in patients with schizophrenia when compared to normal controls. It is important to note that this increase, when corrected for age, was only significant in the group of patients aged between 20 and 29 years, suggesting that this change appears early in the course of the illness (11), but could be concealed later on by other brain changes. Our findings of no significant correlation between ventricular enlargement and duration of illness have been reported by others (21). However, Rubin *et al* (14) in a study of 27 newly diagnosed individuals with schizophrenia and 24 healthy volunteers found no enlargement of the lateral ventricles and only a trend towards enlargement of the third ventricle in the patients. They also found quite severe sulcal enlargements as well as smaller brain volume, shorter brain length and possible left temporal lobe reduction in first-episode schizophrenia. All of these results suggest than at least macroscopic impairment was confirmed mainly to

cortical structures at this early stage of disease.

Other researchers have reported no difference between the size of the ventricles in patients with schizophrenia when compared to healthy controls but the ventricles were larger than those observed in patients suffering from other diseases (4).

Degreef *et al* (10) have reported an increase in the size of the left lateral ventricle but not of the right ventricle. Schwarzkopf *et al* (22) found an increase in left lateral ventricle and in third ventricle size in 36 men with schizophrenia with familial history of the disease (22). In our study as well as in that of Jones *et al* (23) ventricular enlargements were not correlated with the familial history of the patients.

Flaum *et al* (24) reported that the increase in ventricular: brain ratio was observed preferentially in men with schizophrenia. However, our result did not show any sex preference.

In spite of the fact that ventricular enlargement is one of the most consistent anomaly reported in schizophrenia it is not known when in the course of the disease it is developed (25).

Ventriculomegali has been associated with negative symptoms, poor response to neuroleptics, and cognitive damage (26), but some researchers have not found any association (27, 28, 29). Contrary to the report of Bogerts *et al* (30) we could not detect any significant difference between CT measurements and the results of PANSS and BPRS. Lewis (31) reviewed 41 CT studies in patients with schizophrenia and found that in only 5 of 18 reports a significant correlation between ventricular enlargement and negative symptoms was detected. But Marks and Luchins (32) after reviewing 28 CT reports found than in 18 a significant correlation was observed between ventriculomegali and increase of negative symptoms.

The increment in the width of fissura Sylvii in both hemispheres that we have detected has been reported previously by Schwartz *et al* (8) who considered these findings as the result of the decrease in the size of the superior temporal gyrii. A wider left fissura Sylvii with no alterations in the right side has also been reported (14). Contrary to our findings of a predominance in women, Rubin *et al* (14) reported that the sulcal enlargenment was more pronounced in male patients. A decrease in the width of fissura Sylvii has also been found (33, 34).

Our findings of a significant enlargement of lateral ventricles and in the width of fissura Sylvii lend support to the hypothesis that a degenerative pathological process is responsible for these structural abnormalities. However, this and other studies make evident that any brain pathology in schizophrenia is subtle and appears as quantitative differences in the midst of often wide normal variations. On the other hand, schizophrenia is a heterogeneous disorder clinically and may be also aetiologically heterogeneous; there-

fore any abnormality will be difficult to demonstrate and replicate and will require of many well designed studies to show which alteration will be more marked in any particular subgroup of patients.

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