

Magnetic resonance imaging of brain anomalies in adult and pediatric schizophrenia patients: Experience of a Romanian tertiary hospital

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Abstract. Schizophrenia is a severe mental illness with a significant impact on the life of both the patient and the patient's family. Magnetic resonance imaging has proven a useful tool for studying structural changes of the brain in schizophrenia. However, interpreting the published literature presents several challenges. Despite thorough research in recent years, which has included anatomopathological, imaging, electrophysiological, and genetic studies, the intimate pathophysiological mechanisms of this disease are not yet fully elucidated. The present study included patients with schizophrenia diagnosed in the psychiatric clinics from the 'Prof. Dr. Alexandru Obregia' Clinical Psychiatry Hospital between September 2019 and December 2020. Three Tesla magnetic resonance neuroimaging studies were performed. In a significant number of cases, the neuroimaging studies showed association of cerebral modifications such

as enlargement of the Virchow spaces, lesions of the white matter with demyelinating appearance, and inflammatory sinus reactions. Cortical atrophy and hemosiderotic spots were present in a statistically significant proportion in the patient group with an age range of 29-61 years. MRI is indicated as a useful technique in the follow-up process of schizophrenia patients. However, whether the anomalies revealed in this disorder can be utilised as diagnostic biomarkers is still being debated.

Introduction

Schizophrenia is one of the most common psychiatric disorders, with an annual incidence rate of approximately 0.05% (1). Although studied for over a century, the neuropathology of schizophrenia is still unknown (2). Schizophrenia is thought to be caused by a complex interplay of genetic and environmental risk factors that affect early brain growth and biological adaptation to life experiences (3,4). With the development of computed tomography (CT) and magnetic resonance imaging (MRI) technologies, the number of imaging studies performed in patients with schizophrenia has increased. Numerous neuroimaging studies have identified structural and functional abnormalities in patients with schizophrenia, but no diagnostic value can be attributed to any change. Thus, studies on brain volume did not show statistically significant differences in MRI investigations between patients with schizophrenia and normal control subjects. Other cerebral anomalies reported in some studies on the imaging aspects of patients with schizophrenia were enlargement of the lateral

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ventricles or only their temporal horn, enlargement of ventricle three or four, and a reduction in the volume of the temporal or frontal or parietal or occipital brain lobes (5-7). In some studies changes in the volume of the corpus callosum have also been reported (8-10). A total of 92% of imaging studies in patients with schizophrenia reported doubling of the septum pellucidum (11,12). The presence of enlarged Virchow spaces was reported in a significant proportion in patients with schizophrenia compared to the control group (30.3%) (13).

Najjar and Pearlman described, in a review of 15 imaging studies that included 792 patients with schizophrenia, the presence of a significant proportion of white matter abnormalities, which would suggest the existence of structural and functional dysconnectivity, even in the early stages of psychoses (14). Changes in the structure of the white matter may influence perception, thought and behavior (15).

Imaging studies did not show significant differences between patients in the first psychotic episode and those with chronic forms of schizophrenia except for an expansion of the volume of the lateral ventricles (16-19).

Schizophrenia in pediatric patients described as early onset schizophrenia (EOS), ages 13-18, and very early onset schizophrenia (VEOS), ages <13, is observed less frequently than adult-onset schizophrenia, but is generally more severe, from both a clinical and neurobiological perspective (20). Findings from the structural MRI studies of patients with EOS and VEOS have shown smaller total cerebral volume in VEOS patients compared to controls (21,22), increased lateral ventricular volume (21), reduced thalamic volume (21,23), and enlarged cavum septum pellucidum in VEOS vs. controls (24). Information provided by longitudinal studies has shown that in EOS and VEOS patients decrements in grey matter volume in frontal, temporal and parietal cortices were identified over time (25). It is difficult to determine how medication affects the process of grey matter loss in schizophrenia (26). Medication-naïve childhood-onset schizophrenia (COS) subjects are difficult to identify due to the severity of the disorder (27). Grey matter loss and ventricular enlargement have been identified in many adult schizophrenia trials using brain MRI, which are progressive (19,28-31). In the literature, it is speculated that since puberty is a period of massive brain reorganization, the grey matter changes in COS would be more pronounced than in the schizophrenic adult population, which may be the trigger or the effect of the more serious COS phenotype (32). Since there are currently no methods for reliably identifying and studying individuals until the onset of schizophrenia, determining when the structural brain abnormalities occurred is difficult (31). Differences in brain volumes between schizophrenic patients and healthy adults are also evident around the time patients receive treatment (11,33). Additionally, it has been found that in schizophrenic individuals, brain volume alterations tend to be most pronounced in the first years of disease (31,34,35).

In this study, neuroimaging studies in adult and pediatric patients with schizophrenia were assessed. The main MRI abnormalities identified in patients with schizophrenia included in the study were: enlarged Virchow spaces, sinusitis, white matter abnormalities, hemosiderotic spots, but also cortical atrophy, cerebral palsy or venous malformations.

Patients and methods

Patient data. Adult and pediatric patients diagnosed with schizophrenia admitted to the 'Prof. Dr. Alexandru Obregia' Clinical Psychiatry Hospital between September 2019 and December 2020 were included in the study. For the inclusion in the study of patients with schizophrenia, a study protocol was used, which included anamnesis data, clinical evaluation with general clinical examination, neurological examination and psychiatric examination in which the scales specific to schizophrenia were applied [PANSS (36), Calgary Scale (37), Sheehan Disability Scale (38), Addenbrooke's Cognitive Examination (39)] and psychological examination. The diagnosis of schizophrenia was established according to DSM-IV-TR and ICD 10 criteria (40,41).

The inclusion of patients in the study was achieved after the patients or legal guardian signed the informed consent. The study was run in accordance with the World Medical Association Declaration of Helsinki and was approved by the Institutional Ethical Board of the institution Clinical Hospital of Psychiatry 'Prof. Dr. Alexandru Obregia'.

Methods. Magnetic resonance imaging 3 Tesla was performed according to the standard protocol, including T1, T2, FLAIR, DWI, ADC, and SWI sequences.

Patients with contraindications for performing MRI, such as cardiac pacemaker, implanted cardiac defibrillator, internal pacing wires, clips such as cerebral, carotid or aortic aneurysm, cochlear implants, any implant held in by magnet, Swan-Ganz catheter, with claustrophobia or a possibly pregnancy, were excluded. After exclusion criteria, 45 patients [21 male and 24 female; age range 13-61 years with a mean age of 26.71 years and a standard deviation (SD)=14.39] with schizophrenia were qualified to be introduced in the study at this stage.

Statistical analysis. For statistical analysis, the data obtained were entered into Excel documents, then transferred to the IBM SPSS 22 (SPSS, Inc.) statistical analysis program. Statistical analysis was performed using JASP 0.14.1.0 software. The χ^2 test and Bayesian contingency Table test were performed. These statistical tests were applied to verify the existence of relationships between variables, personal characteristics of patients and brain abnormalities encountered in schizophrenia. $P < 0.05$ was considered to indicate statistical significance.

Results

Patient data. The study included 45 patients (21 male and 24 female), with an age range of 13-61 years (mean age, 26.71 years and SD of 14.39).

MRI anomalies. The MRI studies showed variable anomalies, alone or in different combinations: enlarged Virchow spaces in 44 patients, sinusitis in 27 cases, white matter abnormalities in 16 subjects, hemosiderotic spots in 2 patients, cortical atrophy in 4 cases, lacuna and doubling septum pellucidum in 3 patients, respectively, mega cisterna magna and calcification of the falx cerebri in 2 subjects, respectively, and 1 patient had a venous malformation

Table I. Contingency table concerning the association between sex and brain abnormalities in the patients with schizophrenia (N=45).

Variables	Sex		Total
	M	F	
Enlarged Virchow spaces			
Absent	1	0	1
Present	20	24	44
Total	21	24	45
White substance abnormalities			
Absent	15	14	29
Present	6	10	16
Total	21	24	45
Sinusitis			
Absent	6	12	18
Present	15	12	27
Total	21	24	45
Mega cisterna magna			
Absent	19	24	43
Present	2	0	2
Total	21	24	45
Doubling septum pellucidum			
Absent	19	23	42
Present	2	1	3
Total	21	24	45
Cortical atrophy			
Absent	20	21	41
Present	1	3	4
Total	21	24	45
Hemosiderotic spots			
Absent	19	24	43
Present	2	0	2
Total	21	24	45
Lacuna			
Absent	21	21	42
Present	0	3	3
Total	21	24	45
Venous malformation			
Absent	21	23	44
Present	0	1	1
Total	21	24	45
Calcification of the falx cerebri			
Absent	19	24	43
Present	2	0	2
Total	21	24	45

(Table I). A total of 26 of the patients had both enlarged Virchow spaces and sinusitis, and 8 of the patients had both sinusitis and white substance abnormalities.

Considering sex of patients, 24 women and 20 men had enlarged Virchow spaces, 6 men and 10 women had white

Table II. The χ^2 tests concerning the association between sex and brain abnormalities in the patients with schizophrenia (N=45).

Variables	Value	df	P-value
Enlarged Virchow spaces	1.169	1	0.280
White substance abnormalities	0.838	1	0.360
Sinusitis	2.143	1	0.143
Mega cisterna magna	2.392	1	0.122
Doubling septum pellucidum	0.517	1	0.472
Cortical atrophy	0.828	1	0.363
Hemosiderotic spots	1.607	1	0.205
Calcification of the falx cerebri	2.392	1	0.122
Lacuna	2.813	1	0.094
Venous malformation	0.895	1	0.344

matter abnormalities, but without any statistical significance ($P>0.05$) (Tables I and II).

Sinusitis was one of the most common abnormalities in our sample, but it did not predominate statistically significantly in either sex, although the abnormality was present in 15 men and 12 women ($P>0.05$) (Tables I and II).

Calcification of the falx cerebri, mega cisterna magna and hemosiderotic spots were present in 2 of the men, respectively. However, this aspect is not characteristic of the male group as no significant association was found between these variables ($P>0.05$) (Tables I and II).

Lacuna and venous malformation were present in 3 and 1 of the women, respectively; however, no significant correlation was found between sex and the two anomalies ($P>0.05$) (Tables I and II).

Doubling septum pellucidum and cortical atrophy were present in both men and women; however, there were no significant differences between them ($P>0.05$) (Tables I and II).

Relationship between age and brain abnormalities. Enlarged Virchow spaces, sinusitis and white substance abnormalities were the most common abnormalities of the brain by age category albeit these abnormalities were not a characteristic of any age category from a statistical point of view ($P>0.05$) (Tables III and IV).

Mega cisterna magna (4 participants) and calcification of the falx cerebri, (2 participants) and lacuna were present in the second age category (13-28 years) more frequently than in the first age category (29-61 years) albeit there were no statistically significant differences between the two age categories ($P>0.05$) (Tables III and IV).

Cortical atrophy and hemosiderotic spots were present in the second age category (29-61 years) (8 patients) more frequently than in the first category (13-28 years) (1 patient) and there are statistically significant differences between the two age categories ($P<0.05$) (Tables III and IV). The statistical significance of cortical atrophy and hemosiderotic spots by age category is shown in Table V (BF_{10} independent multinomial cortical atrophy=4.462, BF_{10} independent multinomial hemosiderotic spots=8.675). In addition, in Figs. 1 and 2, it can

Table III. Contingency table concerning the association between age and brain abnormalities in the patients with schizophrenia (N=45).

Variables	Age range		Total
	13-28 years	29-61 years	
Enlarged Virchow spaces			
Absent	1	0	1
Present	24	20	44
Total	25	20	45
White substance abnormalities			
Absent	19	10	29
Present	6	10	16
Total	25	20	45
Sinusitis			
Absent	11	7	18
Present	14	13	27
Total	25	20	45
Mega cisterna magna			
Absent	25	18	43
Present	0	2	2
Total	25	20	45
Doubling septum pellucidum			
Absent	23	19	42
Present	2	1	3
Total	25	20	45
Cortical atrophy			
Absent	25	16	41
Present	0	4	4
Total	25	20	45
Hemosiderotic spots			
Absent	24	16	40
Present	1	4	5
Total	25	20	45
Lacuna			
Absent	23	19	42
Present	2	1	3
Total	25	20	45
Venous malformation			
Absent	24	20	44
Present	1	0	1
Total	25	20	45
Calcification of the falx cerebri			
Absent	25	18	43
Present	0	2	2
Total	25	20	45

be seen that the differences between the two age categories in terms of the anomalies discussed are strongly supported by the data collected, $BF_{10} > BF_{01}$.

Table IV. The χ^2 tests concerning the association between age and brain abnormalities.

Variables	Value	df	P-value
Enlarged Virchow spaces	0.978	1	0.323
White substance abnormalities	0.841	1	0.175
Sinusitis	1.201	1	0.273
Mega cisterna magna	2.188	1	0.139
Doubling septum pellucidum	0.311	1	0.577
Cortical atrophy	4.590	1	0.032
Hemosiderotic spots	5.881	1	0.015
Calcification of the falx cerebri	2.392	1	0.122
Lacuna	0.313	1	0.564
Venous malformation	0.978	1	0.322

Table V. Bayesian contingency table tests and the association between age, cortical atrophy, and hemosiderotic spots.

Variable	Value
BF_{10} independent multinomial cortical atrophy	4.462
N	45
BF_{10} independent multinomial hemosiderotic spots	8.675

Relationship between sex and brain abnormalities in children. The study included 25 pediatric patients (12 boys and 13 girls). The age interval was 13-18 years (mean age of 15.08 years; SD of 1.68). Of the 25 patients, 24 had enlarged Virchow spaces, 14 had sinusitis, 6 had white substance abnormalities, 1 had hemosiderotic spots, 2 had lacuna and doubling septum pellucidum, respectively, and 1 of the participants had venous malformation.

Although, 13 of the girls in the sample and 11 of the boys had enlarged Virchow spaces, this brain abnormality no longer predominated in one of the sexes from a statistical point of view ($P > 0.05$) (Tables VI and VII).

Sinusitis was one of the most common abnormalities in patients in our sample, but did not predominate statistically significantly in either sex ($P > 0.05$) (Tables VI and VII).

Discussion

The results obtained in patients of the present study partially overlap with those reported in the literature, in the sense that the enlargement of the Virchow spaces was observed in a high percentage of cases, as was the case for white matter demyelinating lesions, and cortical atrophy. Akhtar *et al* (13) conducted a comparative study, with a group of 33 schizophrenic patients and a control group of 33 healthy individuals with a mean age of 30 years, in order to determine whether there is any structural changes in brain matter. Enlarged Virchow spaces were identified in 10 (30%) of all those with schizophrenia and zero of the control subjects. In addition, in that study there were no significant differences by sex, compared to the control group or between individuals in the same group. The presence

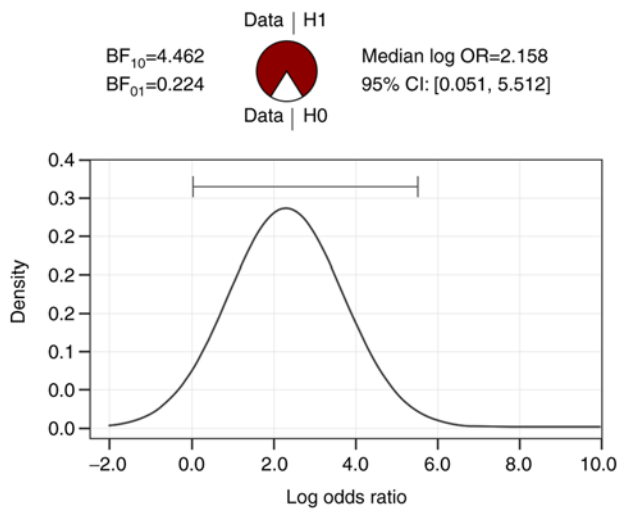


Figure 1. Graphical representation of the relationship between age and cortical atrophy (Bayesian test).

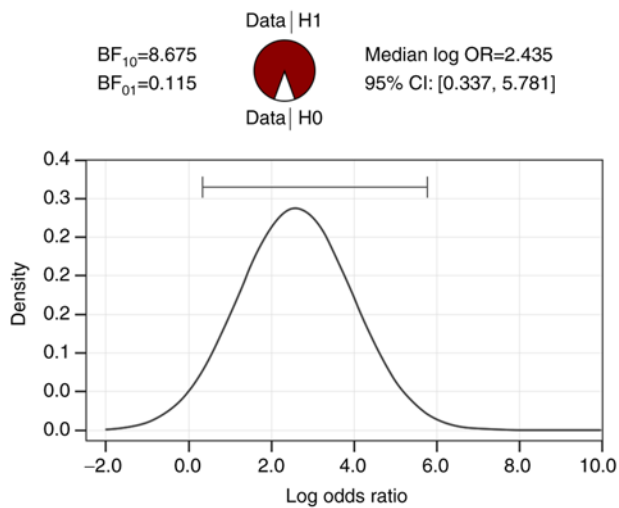


Figure 2. Graphical representation of the relationship between age and hemosiderotic spots (Bayesian test).

of enlarged Virchow spaces in adults was associated with different situations including vascular ectasia, CSF pulsations, abnormal arterial wall permeability, dementia, and hypertension (42,43). Wuerfel *et al* suggested a role of Virchow spaced in inflammatory processes of the brain (44). The significance of enlarged Virchow spaces in children and adolescents is not clear. A study on children with autism spectrum disorder (ASD) showed an increased incidence of enlarged Virchow spaces in ASD children compared with control group; this anomaly was correlated with the expression of symptoms and with a low adaptative functioning (42).

Sinusitis was also reported in 10 of the cases of schizophrenia and 22 of the individuals in the control group, while in our case sinusitis had a frequency of 60% of the total number of patients. Davis *et al* (45) suggested that the MRI shows in patients with schizophrenia a slight, but substantial white matter decrease. Of the 45 patients in the present study, 16 patients had white matter abnormalities, which means a percentage of 35.5%.

Table VI. Contingency table for the association between sex and brain abnormalities in children (N=25).

Variables	Sex		
	M	F	Total
Enlarged Virchow spaces			
Absent	1	0	1
Present	11	13	24
Total	12	13	25
White substance abnormalities			
Absent	9	10	19
Present	3	3	6
Total	12	13	25
Sinusitis			
Absent	5	6	11
Present	7	7	14
Total	12	13	25
Mega cisterna magna			
Absent	12	13	25
Present	0	0	0
Total	12	13	25
Doubling septum pellucidum			
Absent	10	13	23
Present	2	0	2
Total	12	13	25
Cortical atrophy			
Absent	12	13	25
Present	0	0	0
Total	12	13	25
Hemosiderotic spots			
Absent	12	12	24
Present	0	1	1
Total	12	13	25
Calcification of the falx cerebri			
Absent	12	13	25
Present	0	0	0
Total	12	13	25
Venous malformation			
Absent	12	12	24
Present	0	1	1
Total	12	13	25
Lacuna			
Absent	12	11	23
Present	0	2	2
Total	12	13	25

In a large number of cases, the presence of a sinus reaction has been identified, both in pediatric and adult patients. Findings have shown there is an association between mental disorders and sinusitis (46,47). The link between schizophrenia and sinusitis could be investigated in order to demonstrate whether patients with schizophrenia

Table VII. The χ^2 test for the association between sex and brain abnormalities in children.

Variable	Value	df	P-value
Enlarged Virchow spaces	1.128	1	0.288
Sinusitis	0.051	1	0.821

have a predisposition to developing sinus disorders or whether they develop a chronic inflammatory process. Mega cisterna magna, calcification at falx cerebri level, doubling of the septum pellucidum and gap-type lesions were more frequent in the age category 29-61 years, with no statistically significant differences between the two age categories. Cortical atrophy and hemosiderotic spots were more frequently described in patients aged 29-61 years, with statistically significant differences between the two age categories. Regarding the hemosiderotic spots, lacuna, the venous malformation and the calcification of the falx cerebri found on MRI in the current study, few reports in the literature discuss their manifestation and it is reasonable to conclude that they are not frequent abnormalities of the brain in patients with schizophrenia.

The occurrence of cortical atrophy and the abnormal cavum septum pellucidum are the most common changes on MRI in patients with schizophrenia, according to the literature. Given that 25 of the 45 patients in the current study were children, it is not surprising that only 7 (15.5%) of them documented cortical atrophy or the presence of double septum pellucidum. Childhood-onset schizophrenia (COS) exhibits brain anatomic abnormalities that are close to those observed in adult populations, suggesting that there is a general continuity between these exceptional childhood cases and adult schizophrenia populations.

The research included patients with schizophrenia who were already taking antipsychotic treatment. Concerning utilization of antipsychotic medications by a large number of participants in neuroimaging trials, the effect of antipsychotic medications as a cause of MRI changes was not previously explored (48). Lieberman *et al* concluded that prescribing haloperidol to patients caused a marked reduction in the grey matter after 12 and 52 weeks, but no reduction was observed in patients who were prescribed olanzapine. Patients were investigated using MRI brain imaging (49). The brain seems to be more damaged after taking typical antipsychotics than atypical ones. This is not the only study reported in medical literature that observed the impact of antipsychotics upon the brain structure. However, data from studies of wider groups of participants shows a progressive association between antipsychotic usage and brain volumetric decrease. Cahn *et al* reported MRI modifications in 34 schizophrenic patients undergoing treatment with typical and atypical antipsychotics, modification such as increased volume of lateral ventricles and decreased brain volume, especially in grey matter. Patients were prospectively studied for 16 weeks and compared to a control group that did not receive any antipsychotic treatment (50). In a study of

18 antipsychotic-naïve schizophrenia patients and 18 stable controls, Jayakumar *et al* (51) found gray-matter volumetric decreases and higher cerebrospinal fluid volumes, as did Davatzikos *et al* (52).

Since prior imaging was not available for comparison, the causal relationship between schizophrenia and observed brain changes could not be determined. The relatively small number of investigated cases did not allow the establishment of imaging abnormalities with the role of biomarker, thus an extension of the number of investigated cases being necessary, as well as the comparative evaluation with a similar group of healthy subjects. To create a link between schizophrenia and brain structural abnormalities, larger longitudinal studies with functional imaging are needed.

In summary, MRI can be a helpful method in identifying brain changes in patients with schizophrenia and can also contribute to establishing a long-term prognosis for them. Additionally, MRI may be used to make a differential diagnosis between organic psychoses and those that do not have a neurological substrate (53,54).

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FPI conceived and designed the study, wrote the manuscript, contributed in all stages of the article. MCM analyzed and collecting data regarding MRI findings. MB performed statistical analysis and was involved in revising the manuscript critically for important intellectual content. EA and FL contributed to the data collection and interpretation. FR contributed to reviewing the data and editing of the manuscript. RC confirmed the authenticity of all the imaging investigations and interpreted the results. AMC finalized the analysis and gave the final approval of the version to be published. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of 'Prof. Dr. Alexandru Obregia' Clinical Hospital of Psychiatry, Bucharest, Romania (approval no. 10/21.03.2018). Written informed consent was obtained from each patient/legal guardian of each patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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