BRAIN ABNORMALITIES IN SCHIZOPHRENIA

A qualitative comparative study of schizophrenic patients and control individuals assessed by magnetic resonance imaging

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INTRODUCTION

With the development and application of neuroimaging techniques, the direct study of the structure and cerebral functions in vivo in patients with schizophrenia has suggested the existence of an anatomic substrate related to the illness. Since 1984, when Smith et al. [24] first examined cerebral morphology using Magnetic Resonance Imaging (MRI) on 9 schizophrenic patients and 5 healthy individuals, a series of quantitative MRI studies have clearly shown structural brain abnormalities in cases of schizophrenia. The most frequently encountered anomalies have proved to be the enlargement of the lateral and third ventricles, and the reduction either in the total volume of the temporal lobe or in one or more of its structures (Ammon’s horn, amygdala and para-hippocampal gyrus). There has also been evidence for frontal, parietal, occipital lobes and subcortical abnormalities (thalamus, corpus callosum, basal ganglia and cavum septum pellucidum) [19, 22], although these findings are somewhat less consistent. However, few previous studies have been done adopting a qualitative approach with MRI. Some of them have focused on a single abnormality [5, 6, 23], others have considered a wider range of structural anomalies. In a case-control study, Lieberman et al. [16] reported a higher prevalence of brain morphological anomalies in a group of schizophrenic patients, considering the overall rates of these anomalies but also examining one by one for four brain regions (lateral ventricles, third ventricle, frontal and parietal cortex, and medial temporal structures). Although using different methods, Lewine et al. [13] confirmed these results. In their study, Lawrie et al. [12] reported a

SUMMARY

The present study examined, by means of Magnetic Resonance Imaging (MRI), the qualitative brain abnormalities in a group of 58 schizophrenic patients compared to a group of 58 matched control individuals. The possible relationships between these abnormalities and the demographic and clinical features of the participants in the study were also investigated.

Schizophrenic patients presented a higher percentage of bland-moderate enlargement of the periencephalic-subarachnoid spaces (p=0.01) and a widespread cerebral atrophy, the latter below the threshold of significance (p=0.06).

In the subset of patients with ventricular asymmetry (right larger than left) the age was significantly lower compared to the age of patients without this abnormality (p=0.04).

In the subset of patients with cerebellar cisterns enlargement the age as well as the age of onset was higher in comparison to the one of patients without this abnormality (p=0.02; p=0.006).

Taking together with previous studies, these findings underline the importance of qualitative assessment of brain morphology in research and clinical evaluation of patients with schizophrenia.

Key words: schizophrenia, MRI, subarachnoid space, cerebral atrophy.

RÉSUMÉ

Anomalies cérébrales dans la schizophrénie : étude qualitative comparative entre patients schizophrènes et sujets contrôles par IRM

La présente étude a comparé par IRM, les anomalies qualitatives cérébrales chez 58 patients psychotiques et 58 sujets contrôles. L'association entre les anomalies et les variables démographiques et cliniques des participants à l'étude a été également analysée. Les sujets psychotiques ont présenté, plus fréquemment que les sujets contrôles, un élargissement des espaces sous-arachnoïdiens périencéphaliques (p=0.01) et une atrophie cérébrale diffuse, bien que cette dernière association soit non significative (p=0.06). Dans le sous-groupe de patients qui présentaient une asymétrie ventriculaire droite prédominante, l'âge moyen était significativement plus bas par rapport à l'âge des sujets psychotiques sans cette anomalie (p=0.04); dans le sous-groupe de patients qui présentaient un élargissement des espaces sous-arachnoïdiens péricérébelleux, l'âge moyen et l'âge moyen d'apparition de la maladie étaient plus élevés que ceux des patients psychotiques sans cette anomalie (p=0.02 ; p=0.006).

En accord avec les précédentes études quantitatives, ces résultats ont confirmé la présence d'un agrandissement des espaces sous-arachnoïdiens périencéphaliques chez les sujets psychotiques par rapport aux sujets contrôles, en l'absence d'atrophie cérébrale.

Mots-clés : schizophrénie, IRM, espaces sous-arachnoïdiens, atrophie cérébrale.

INTRODUCTION

With the development and application of neuroimaging techniques, the direct study of the structure and cerebral functions in vivo in patients with schizophrenia has suggested the existence of an anatomic substrate related to the illness. Since 1984, when Smith et al. [24] first examined cerebral morphology using Magnetic Resonance Imaging (MRI) on 9 schizophrenic patients and 5 healthy individuals, a series of quantitative MRI studies have clearly shown structural brain abnormalities in cases of schizophrenia. The most frequently encountered anomalies have proved to be the enlargement of the lateral and third ventricles, and the reduction either in the total volume of the temporal lobe or in one or more of its structures (Ammon’s horn, amygdala and para-hippocampal gyrus). There has also been evidence for frontal, parietal, occipital lobes and subcortical abnormalities (thalamus, corpus callosum, basal ganglia and cavum septum pellucidum) [19, 22], although these findings are somewhat less consistent. However, few previous studies have been done adopting a qualitative approach with MRI. Some of them have focused on a single abnormality [5, 6, 23], others have considered a wider range of structural anomalies. In a case-control study, Lieberman et al. [16] reported a higher prevalence of brain morphological anomalies in a group of schizophrenic patients, considering the overall rates of these anomalies but also examining one by one for four brain regions (lateral ventricles, third ventricle, frontal and parietal cortex, and medial temporal structures). Although using different methods, Lewine et al. [13] confirmed these results. In their study, Lawrie et al. [12] reported a
higher prevalence of generalised cerebral atrophy, high-intensity signal (HIS) foci, cerebellar atrophy, and other gross structural abnormalities in schizophrenic patients compared with healthy individuals. Galderisi et al. [10] found that the only abnormality that was significantly more frequent in schizophrenic patients than in control subjects was the enlargement of the lateral ventricles. Taking into consideration the foregoing, the main target of our project was to examine, by qualitative evaluation of MRI scans, the rates of cerebral abnormalities in a group of schizophrenic patients compared to a group of control individuals. Relationships between these anomalies and the demographic (age) and clinical variables (duration of illness and age at onset) of the participants in the study were also investigated. In order to minimize variability due to gender differences or any possible effect of ageing on the cerebral structures, we included in our study only male subjects aged 18-45 years.

METHODS

Subjects

The study sample consisted of 58 male subjects diagnosed with schizophrenia or other related disorders of the schizophrenia spectrum, including: 45 patients with chronic schizophrenia (paranoid=18; undifferentiated=12; disorganized=8; catatonic=4; and residual=3), 3 patients with first-episode of schizophrenia, 6 patients with schizophreniform disorder and 4 patients with schizoaffective disorder, consecutively admitted to the III Psychiatric Clinic, University of Rome “La Sapienza”, undergoing MRI. The mean age of the patients was 31.12±9.67 years (mean duration of illness: 10±8.56 years; mean age at onset: 21.21±7.24 years). Psychiatric diagnoses were determined according to DSM IV criteria.

The control group comprised 58 male individuals (mean age: 32.53±7.92 year), with no past or present psychiatric pathologies in their medical history. They were recruited from the I Medical Clinic, Magnetic Resonance Imaging Unit, University of Rome “La Sapienza” and screened for major psychiatric and medical illness prior to MRI exam.

Exclusion criteria for all subjects (patients and controls) included: alcohol or drug abuse (past or present), dementia, epilepsy, Parkinson’s disease or other chronic neuromedical illness, neurosurgery, mental retardation, tumours, or any other conditions unsuitable for MRI.

In order to exclude any effect of ageing on cerebral structures, only individuals aged 18-45 years were included in this study.

Further information concerning the clinical and demographic characteristics of the subjects were obtained by examining their clinical records.

Both patients and controls gave their informed consent.

MRI evaluation

MRI scans were carried out with 1 Tesla Philips Gyroscan equipment, with sequences in conventional spin echo (SE) T1-weighted (TR=550/TE=15), turbo spin echo (TSE) T2-weighted (TR=3000/ TE=90) and fluid-attenuated inversion recovery (FLAIR) (TR=5000/TE=100/TI=1900) in the axial and coronal planes. On some individuals, sagittal plane sequences were used. Slice thickness varied from 4 to 6 mm with a gap of 0.4.

In the controls and only for suspected ischemic and/or neoplastic lesions, post-contrast T1-weighted images were obtained.

Two experienced neuroradiologists, blinded to the diagnosis of the individuals analysed in this study, performed independently the evaluation of MRI scans. They reported all the morphological abnormalities noticed, subsequently divided as follows: 1) ventricular abnormalities (enlargement and/or asymmetry); 2) bland-moderate enlargement of the pericerebellar-subarachnoid spaces; 3) bland-moderate enlargement of the pericerebellar-subarachnoid spaces; 4) cerebral atrophy; 5) cerebellar atrophy; 6) high-intensity signal lesions; 7) mid-line development abnormalities (cavum septum pellucidum, cavum vergae and septal cysts); 8) cystic lesions; and 9) empty sella.

The diagnosis of cerebral and/or cerebellar atrophy was confirmed only in case of severe enlargement of pericerebellar and/or pericerebellar subarachnoid spaces.

High intensity signal lesions were defined as at least 4 mm in diameter.

Non-fusion of the septum pellucidum was rated as cavum septum pellucidum (where incomplete) or cavum vergae (where complete).

Perfect agreement (k=1) was reached, either in patients or in controls, for ventricular abnormalities (enlargement and/or asymmetry), cerebellar atrophy, high intensity signal lesions, mid-line development abnormalities (cavum septum pellucidum, cavum vergae and septal cysts), cystic lesions and empty sella; perfect agreement (k=1) has been achieved, only in controls, for bland-moderate enlargement of the pericerebellar-subarachnoid spaces and for cerebral atrophy. The kappa for bland-moderate enlargement of the pericerebellar-subarachnoid spaces in patients and in controls were 0.94 and 0.97 respectively; the kappa for bland-moderate enlargement of the pericerebellar-subarachnoid spaces and for cerebral atrophy, in patients, was 0.98 in both ratings. In case of discrepancy the final result was reached according to the senior observer.

Statistical analysis

The following statistical analyses were carried out: 1) comparison between patients and control individuals on the frequency of MRI abnormalities ($\chi^2$ test and Fisher’s exact test); and 2) evaluation of differences on continuous variables (such as age, age at onset, and duration of illness) between patients with abnormalities and patients without abnormalities, and, considering only age, between control individuals with abnormalities and control individuals without abnormalities (one-way ANOVA). In each analysis, probability level was $P<0.05$. 

Inter-observer reliability of the two radiologists was determined by computing the interclass correlations (Cohen’s kappa) of their ratings [21].

RESULTS

Comparison of the frequency of cerebral morphological abnormalities in schizophrenic patients and control individuals.

Overall, the presence of cerebral morphological abnormalities was confirmed in 28 patients (48.2%) and in 28 (48.2%) control individuals.

After comparing the frequency of each abnormality in patients and controls, the following results emerged:

1) There was a higher percentage of bland-moderate enlargement of the periencephalic-subarachnoid spaces in patients [12 out of 58 (20.6%)] than in control individuals [3 out of 58 (5.1%)], with a statistically significant difference between the two groups ($P=0.02$) (table I).

2) Generalized cerebral atrophy was found in 9 individuals (7.7%), with a different frequency in each group [patients=7 out of 58 (12.0%); control individuals=2 out of 58 (3.4%)] and with a difference that was close to statistical significance ($P=0.06$) (table I).

3) There was a higher percentage of cystic lesions (pineal and arachnoid) among the control individuals [7 out of 58 (12.0%)] than among patients [1 out of 58 (1.7%)], with a statistically significant difference between the two groups ($P=0.02$) (table I).

For all the other cerebral morphological abnormalities, no statistically significant difference between the two groups was found.

Comparative analysis by clinical-demographic variables of schizophrenic patients/control individuals with abnormalities and schizophrenic patients/control individuals with no abnormalities.

The two groups (patients and controls) were divided into subgroups for each brain abnormality. One-way ANOVAs were carried out on age, age at onset, and duration of illness, with MRI abnormalities as the grouping factor.

A comparison of age variability between patients with abnormalities and patients with no abnormalities gave the following results:

1) In the subgroup of patients with ventricular asymmetry (n=7), right larger than left, the mean age was significantly lower compared with the age of patients without this abnormality (n=51) ($24.28\pm5.93$ vs $32.05\pm9.74$; $F=4.20$, d.f.=1, $P=0.04$) (table II).

2) In the subgroup of patients with a bland-moderate enlargement of the pericerebellar-subarachnoid spaces (n=4), the mean age was higher compared with the age of patients without this

Fig. 1 – Coronal and axial magnetic resonance images from three different subjects (c and d from the same subject). a) Coronal T1-weighted MR image showing moderate asymmetrical temporal atrophy (right more atrophic). b) Coronal T1-weighted MR image showing a bland periencephalic-subarachnoid spaces enlargement, primarily in the frontal region. c) Axial T1-weighted MR image showing a cavum vergae. d) Axial T1-weighted MR image showing a cavum vergae and a cyst of the septum pellucidum.
TABLE I – Qualitative abnormalities on routine MRI examination in patients with schizophrenia and normal controls.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Patients</th>
<th>%</th>
<th>Normal controls</th>
<th>%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular enlargement</td>
<td>8</td>
<td>13.79</td>
<td>4</td>
<td>6.89</td>
<td>0.36</td>
</tr>
<tr>
<td>Cerebral atrophy</td>
<td>7</td>
<td>12.06</td>
<td>2</td>
<td>3.44</td>
<td>0.06</td>
</tr>
<tr>
<td>PESSE</td>
<td>12</td>
<td>20.68</td>
<td>3</td>
<td>5.17</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>PCSSE</td>
<td>4</td>
<td>6.89</td>
<td>1</td>
<td>1.72</td>
<td>0.15</td>
</tr>
<tr>
<td>HIS lesions</td>
<td>4</td>
<td>6.89</td>
<td>1</td>
<td>1.72</td>
<td>0.15</td>
</tr>
<tr>
<td>MDA</td>
<td>1</td>
<td>1.72</td>
<td>3</td>
<td>5.17</td>
<td>0.24</td>
</tr>
<tr>
<td>Cystic lesions</td>
<td>1</td>
<td>1.72</td>
<td>7</td>
<td>12.06</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Empty sella</td>
<td>3</td>
<td>5.17</td>
<td>0</td>
<td>0</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Abbreviations: PESSE, periencephalic-subarachnoid spaces enlargement; PCSSE, pericerebellar-subarachnoid spaces enlargement; HIS lesions, high intensity signal lesions; MDA, midline developmental abnormalities.

3) After comparing the two groups (patients with abnormalities and patients without abnormalities) in terms of age at onset, the results showed that the mean age was higher in the subgroup of patients that showed a bland-moderate enlargement of the pericerebellar-subarachnoid spaces compared with the subgroup without this abnormality (30.50±13.62 vs 20.51±6.23, F=7.93, d.f.=1, P=0.0067) (table II).

A comparison of the two groups on the basis of duration of illness did not reveal any statistically significant difference.

Finally, no statistically significant difference emerged from the comparison of control individuals with abnormality and control individuals without abnormality on the basis of age.

DISCUSSION

The great majority of qualitative MRI studies have reported a higher prevalence of ventricular abnormalities in schizophrenic patients than in healthy individuals [10, 12, 13, 16]. Thus, our findings, which seem to indicate a similar incidence of ventricular abnormalities (enlargement and/or asymmetry) in both groups (schizophrenics and controls), are not consistent with these other investigations. This apparent discrepancy could be at least partially explained by the homogeneity of the groups we examined, and also by the strict criteria we used to define and differentiate the various cerebral morphological abnormalities.

Lieberman et al. [16], who revealed a higher prevalence of ventricular anomalies in the group of schizophrenic patients than in the group of healthy individuals, compared the two groups by examining the enlargement, the asymmetry and possible ventricular shape abnormalities (which we did not consider).

TABLE II – ANOVA on age and age at onset in patients with and without qualitative MRI abnormalities.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Patients (mean±S.D.)</th>
<th>Age at onset (mean±S.D.)</th>
<th>P</th>
<th>Patients (mean±S.D.)</th>
<th>Age at onset (mean±S.D.)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular enlargement</td>
<td>30.25±7.86</td>
<td>18.00±6.65</td>
<td>0.78</td>
<td>21.72±7.26</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>VA (right larger than left)</td>
<td>24.28±5.93</td>
<td>21.49±7.57</td>
<td><strong>0.04</strong></td>
<td>21.22±7.34</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>VA (left larger than right)</td>
<td>37.50±10.78</td>
<td>21.00±6.68</td>
<td>0.17</td>
<td>21.09±7.39</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Cortical atrophy</td>
<td>34.71±11.94</td>
<td>22.00±6.48</td>
<td>0.29</td>
<td>21.33±7.24</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Cerebellar atrophy</td>
<td>34.00</td>
<td>14.00</td>
<td>0.76</td>
<td>20.76±6.42</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>PESSE</td>
<td>34.08±10.78</td>
<td>22.91±9.94</td>
<td>0.23</td>
<td>20.51±6.23</td>
<td><strong>0.006</strong></td>
<td></td>
</tr>
<tr>
<td>PCSSE</td>
<td>41.25±10.53</td>
<td>30.50±13.62</td>
<td><strong>0.02</strong></td>
<td>20.51±6.23</td>
<td><strong>0.006</strong></td>
<td></td>
</tr>
<tr>
<td>HIS lesions</td>
<td>33.75±15.10</td>
<td>23.25±6.55</td>
<td>0.57</td>
<td>21.21±7.30</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>MDA</td>
<td>45.00</td>
<td>21.00</td>
<td>0.14</td>
<td>21.24±7.30</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Cystic lesions</td>
<td>20.00</td>
<td>19.00</td>
<td>0.24</td>
<td>21.47±7.33</td>
<td>0.23</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: VA, ventricular asymmetry; PESSE, periencephalic-subarachnoid spaces enlargement; PCSSE, pericerebellar-subarachnoid spaces enlargement; HIS lesions, high intensity signal lesions; MDA, midline developmental abnormalities.

In the study by Lewine et al. [13], carried out on a group of 175 patients with different psychiatric diagnoses and on 150 healthy individuals, they analysed the overall different incidence of cerebral morphological anomalies in the two groups. However, in accordance with our findings, in the group of schizophrenic male patients with ventricular asymmetry (right larger than left), the average age was significantly lower than in the group of schizophrenic patients without this abnormality.

Lawrie et al. [12] considered the ventricular enlargement together with the enlargement of the subarachnoid spaces, not as a singular anomaly but as indicative of cortical atrophy.

Finally, in the study by Galderisi et al. [10] a higher prevalence of lateral ventricular enlargement was shown in the group of schizophrenic male patients compared to the group of healthy male individuals, only for patients aged more than 41 years or between the ages of 15 and 28 years.

In some previous qualitative studies [10-12, 16], the degree of generalised loss of cerebral substance was evaluated by using different point-scales, considering the enlargement of periencephalic-subarachnoid spaces. Moreover, in case of a very slight enlargement of these spaces, the cerebral atrophy was considered doubtful or bland. In our study, the neuroradiologic diagnosis of cerebral atrophy was confirmed only in case of a severe enlargement of the periencephalic-subarachnoid spaces, while the bland-moderate enlargement of these spaces was considered as a separate morphological abnormality.

The same criteria were used for the qualitative assessment of cerebellar atrophy.

The group of schizophrenic patients included 7 individuals (12.0%) with cerebral atrophy, and 12 individuals (20.6%) with a bland-moderate enlargement of periencephalic-subarachnoid spaces; the equivalent percentages for the control individuals were 3.4% and 5.1%, respectively (table I). These findings suggest a tendency to a more severe cerebellar atrophy (p=0.06) and a higher prevalence of bland-moderate enlargement of periencephalic-subarachnoid spaces (p=0.02) in patients than in control subjects.

Concerning cerebral atrophy, these results seem to confirm those of previous qualitative studies showing an incidence in schizophrenic patients that ranges from 1% to 58% in CT studies [1, 9], and from 4% to 52% in MRI studies [12, 13].

Results concerning the enlargement of periencephalic-subarachnoid spaces seem to confirm those of other important quantitative studies carried out by MRI scans, where the grey-matter volume, white-matter volume and cerebrospinal fluid (CSF) periencephalic and ventricular volume spaces were measured separately [8, 20].

According to some authors, periencephalic-subarachnoid space enlargement, although less commonly studied, may be the single deficit that best discriminates individuals with schizophrenia from healthy comparison samples [2, 14].

Furthermore, some MRI quantitative studies have shown enlarged periencephalic-subarachnoid spaces in siblings of patients with schizophrenia, suggesting that both periencephalic-subarachnoid spaces and ventricular enlargement may represent a genetically influenced trait marker for schizophrenia [3].

In our study, no significant difference was found after comparing on the basis of clinical-demographic variables (age, age at onset, duration of illness), patients with a bland-moderate enlargement of periencephalic-subarachnoid spaces and those without this abnormality (table II).

Furthermore, no significant difference was found when comparing clinical-demographic variables for patients with cerebral atrophy and those without this abnormality (table II).

These results seem to confirm those of previous MRI studies [12, 16, 17], and they may be compatible with the hypothesis of a malformative origin of these alterations, connected to a developmental disorder of the cerebral structures.

Although a prevalence of a bland-moderate enlargement of the pericerebellar-subarachnoid spaces in patients (6.8%) compared with control individuals (1.7%) has been shown, no statistically significant difference was found between the two groups (table I). However, from the comparison of the clinical-demographic variables for patients with an enlargement of pericerebellar-subarachnoid spaces and those without this abnormality, the mean age of patients and the mean age at onset of the illness were higher in the former subgroup (table II).

Although it is difficult to interpret these results, they suggest a cerebellum implication in the neuropathology of schizophrenia, as already demonstrated by various studies, both qualitative [4, 12] and quantitative MRI studies [7, 15, 18].

Concerning controls, they comprised 58 male individuals undergoing MRI for suspected consequences of a recent skull trauma (n=28), or for suspected ischemic and/or neoplastic lesions in subjects with acute dizziness with no other associated neurological signs (n=30), which gave negative results. Of these individuals, five were found with pineal gland cysts and two with arachnoid cysts, presenting a higher prevalence of cystic lesions (12.0%) compared to schizophrenic patients (1.7%), with a statistically significant difference between the two groups (p=0.02) (table II).

In summary, our study seems to demonstrate the prevalence in schizophrenic patients than in controls of a bland-moderate enlargement of periencephalic-subarachnoid spaces and a generalized cerebral atrophy, the latter below the threshold of significance. Although more patients need to be analysed, our findings are compatible with the results of previous quantitative MRI studies, underlining the importance of qualitative assessment of brain morphology in research and clinical evaluation of patients with schizophrenia.

Références

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