

Relation between cerebrospinal fluid, gray matter and white matter changes in families with schizophrenia

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Abstract

Background: Gray matter reduction and ventricular enlargement belong to the best replicated findings in schizophrenia. Brain morphologic changes were also found in non-schizophrenic family members (FM). The intention of this study was to examine whether non-psychotic first-degree relatives reveal similar morphologic changes as schizophrenic patients and how state of genetic loading contribute to these abnormalities.

Methods: Forty-nine schizophrenic patients, 71 non-schizophrenic FM and 48 control subjects took part in this volumetric MRI study. All subjects were between 18 and 59 years old. Dependent variables were gray matter, white matter and total cerebrospinal fluid (CSF) volume, determined by SPM99 segmentation algorithm. As an important part of CSF lateral ventricle volume was determined manually by removing surrounding CSF areas.

Results: In schizophrenic patients compared to controls and non-schizophrenic FM total CSF volumes and lateral ventricles were increased. Gray and, to a lesser degree, white matter volumes were decreased as well. For CSF, gray and white matter there was no significant difference between uni- and multiple affected families. CSF correlated significantly negative with gray matter ($r = -0.78$) and, less intensive, with white matter ($r = -0.40$). There were negative correlations between gray and white matter volume as well ($r = -0.26$). These correlations were not significantly different between the diagnostic groups.

Conclusion: CSF enlargement and gray matter reductions in schizophrenic patients compared to controls and non-affected FM seem to be interdependent findings. However, this correlation is independent of the factor diagnosis and is therefore not specific for schizophrenia.

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1. Introduction

As meta-analyses have reported, it is undisputed that schizophrenic patients show ventricular enlargement and gray matter reductions compared to control subjects (Lawrie and Abukmeil, 1998; McCarley et al., 1999; Wright et al., 2000; Shenton et al., 2001). Beside conventional segmentation methods voxel-based morphometry was used to confirm gray matter volume reductions (Wilke et al., 2001; Ananth et al., 2002).

Lateral ventricles are a part of cerebrospinal fluid (CSF) spaces. It has been shown that total CSF volume is enlarged in schizophrenic patients as well (Gur et al., 1991; Andreasen et al., 1994; Wilke et al., 2001; Hulshoff Pol et al., 2002). Mathalon et al. (2001) demonstrated that CSF and especially ventricular expansion may be progressive. Cannon et al. (1998) showed that sulcal CSF was increased in patients and non-affected siblings compared to controls, while ventricular CSF was only enlarged in patients. On the other hand, Staal et al. (2000) found no significant CSF differences between schizophrenic patients, healthy relatives and controls. Summing up the results of Sharma et al. (1998), Baare et al. (2001), Steel et al. (2002) and McDonald et al. (2002), there are signs that lateral ventricles may form an endophenotype for schizophrenia with values of non-affected relatives ranging between patients and controls and furthermore, that ventricular volumes were increased compared to controls especially in patients with high genetic liability (so-called obligate gene carriers).

Although gray matter deficits were noticed already in first-episode schizophrenia (Zipursky et al., 1998; Gur et al., 1999), they seem to increase with the course of the disease (Hulshoff Pol et al., 2002; Cahn et al., 2002). A progressive component exceeding normal aging changes was also found in a longitudinal MRI study over an average interval of 4 years, demonstrating progressive frontal and temporal gray matter reduction in schizophrenia (Mathalon et al., 2001). Gray matter reductions were found not only in schizophrenic patients, but also in their non-affected family members compared with controls (Cannon et al., 1998; Gogtay et al., 2003).

From the few studies analyzing white matter volumes it is not clear, if there are regional reductions (Cannon et al., 1998; Paillere-Martinot et al., 2001; Hulshoff Pol et al., 2002), no changes (Zipursky et al., 1992) or even increased volumes (Lawrie and Abukmeil, 1998) in schizophrenia.

A subset of the present sample (31 schizophrenic patients, 33 control subjects) was used for a separate study examining aspects of sexual dimorphism in schizophre-

nia (Maric et al., 2003), however, finding no gender differences but a gray matter volume reduction and a CSF volume increase in schizophrenic patients compared to controls.

The present work was intended as a family study, comparing schizophrenic patients with their non-psychotic first-degree relatives on the one side and with control subjects on the other side. Families were classified into unaffected (only one member affected with schizophrenia over three generations) and multiple affected (at least two schizophrenic subjects in subsequent generations). This way, the influence of the extent of genetic loading could be considered.

This study was designed to answer the following questions:

- Is CSF – especially ventricular – enlargement as well as gray matter reduction in schizophrenia replicable in this sample?
- Could the dependent variables CSF, gray and white matter volumes be used to help develop an endophenotype concept for schizophrenia?
- Are lateral ventricle changes more or less pronounced compared to total CSF increase?
- Is there a difference in the extent of CSF, lateral ventricle, gray and white matter changes in schizophrenic patients between unaffected and multiple affected families?
- Is there a correlation between CSF, gray and white matter volume? Is there a differing pattern in this relation between schizophrenic patients, non-schizophrenic FM and controls?

2. Methods

2.1. Patients and control subjects

The present analysis includes the data of 81 individuals examined at the Heinrich-Heine-University Düsseldorf and of 87 individuals examined at the Friedrich-Wilhelms-University Bonn.

Diagnostically the sample consisted of 49 family members with schizophrenia or schizoaffective disorder (ICD-10: F20 ($n = 29$); F25 ($n = 11$)), 71 of their first-degree relatives not affected with schizophrenia (43 from the same generation as the index patient, 28 from the parental generation) and 48 healthy control subjects from families demonstrating no psychiatric disorder over three generations.

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