Acta Clin Croat 2003; 42:333-336 Professional Paper

MAGNETIC RESONANCE IMAGING OF BRAIN AND NEUROPSYCHOLOGICAL TESTING IN MONOZYGOTIC TWINS DISCORDANT FOR SCHIZOPHRENIA

Dalibor Karlović[1], Vlasta Solter[1] and Miljenko Kalousek[2]

[1]University Department of Psychiatry, [2]University Department of Radiology, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – Magnetic resonance imaging (MRI) scanning of the brain, soft neurologic signs, and personality and neuropsychologic assessment were used in a pair of monozygotic twins aged 25, discordant for schizophrenia. Brain MRI showed diffuse cortical atrophy of frontal, parietal and temporal brain lobes in both twins. Coronal plane MRI revealed decreased amygdala and hippocampus, and enlarged third and fourth lateral ventricles in the affected twin.

Key words: *Brain abnormalities; Schizophrenia, pathology; Schizophrenia, genetics; Magnetic resonance imaging, diagnosis; Twins, monozygotic*

Introduction

Schizophrenia is a relatively common disorder with lifetime prevalence in the general population of 1%[1]. The onset of schizophrenia symptoms typically occurs in early adulthood, with a recurrent course and continued disability refractory to treatment in most patients[2]. The disease currently referred to as 'schizophrenia' was first more thoroughly described in the late 19th century under the term 'dementia praecox' in the scientific works of Emil Kraepelin[1]. He separated it from the manic-depressive illness and senile dementias. Later, in 1911, Eugen Bleuler renamed Kraepelin's 'dementia praecox' into 'schizophrenia', to highlight the fact that the disorder produced severe fragmentation of the personality and cognition. The symptoms and signs of schizophrenia are complex, and the diagnostic process was burdened with poor reliability and validity of the diagnosis until modern classification systems such as International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM) have been designed[1,2]. For convenience, the symptoms and signs of schizophrenia can be divided into 'positive' and 'negative' ones. Negative symptoms and signs include aphasia, affective blunting, anhedonia and listlessness, whereas positive symptoms and signs are hallucinations, delusions, disorganized speech, and disorganized/bizarre motor behavior. The etiology of the disorder is multifunctional, implying biochemical and neuroendocrinologic factors as well as brain morphology. The more so, genetic studies have offered several explanations of this complex, perhaps multiple rather than single disease process[2]. Genetic predisposition is the most important known risk factor. Some studies have shown the relative risk to rise 40 times in patients with one or more first degree relatives affected, however, no strongly linked genes have been identified.

Studies using early computed tomography (CT) brain imaging revealed enlarged areas of lateral and third ventricles in schizophrenic patients[3,4]. With the development of nuclear magnetic resonance imaging (NMRI), general reduction in the brain volume and mesial temporal lobe structures (i.e. amygdala and hippocampus) has been demonstrated[4-10]. These findings support the neurodevelop-

Correspondence to: *Dalibor Karlović, M.D., M.S.*, University Department of Psychiatry, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: dalibor.karlovic@zg.htnet.hr

Received May 26, 2003, accepted September 15, 2003

mental hypothesis of schizophrenia[2]. According to this hypothesis, schizophrenia is a sequel of abnormal neuronal migration and/or myelinization, along with excessive apoptosis during the intrauterine development.

In this report, we present findings of psychological examination and MRI brain scanning in monozygotic twins discordant for schizophrenia.

Case Report

A pair of 25-year-old male monozygotic twins discordant for schizophrenia, with university degree of special educators, were examined. They are unemployed, single and live with their parents in a small town near Zagreb. History data revealed normal pregnancy, delivery and early psychomotor development in both twins. During their early childhood, they had all infectious children diseases, received all vaccines, and suffered no medical or psychological problem or disorder. They described their family dynamics as free from any specificities. They were good students and completed their military service. Their medical history contained no data on any substance or alcohol abuse or addiction.

At the age of 21 years, the affected twin manifested initial symptoms of schizophrenia, such as auditory imperative hallucinations, disorganized speech and motor actions, blunted affect, he began to interpret some routine events as special signs, and developed insomnia. According to ICD 10, he met the criteria for schizophrenia, the paranoid-hallucinatory type.

On that occasion, he was hospitalized for the first time. Initially, he was treated as inpatient with a typical antipsychotic agent haloperidol, however, a switch to clozapine as pharmacotherapy was dictated by the poor response of blunted affect, and extrapyramidal side effects with clinical features of akathisia. The initial dose of clozapine was 300 mg, which was subsequently tapered to 100 mg *per* day. Since his first hospitalization, the patient and his twin brother have been continuously attending family psychotherapy once a week, during which period of time he was treated as inpatient on two more occasions, mostly for psychopharmacotherapy titration.

During the last patient's hospital stay, we explained to the twins the study design and medical procedures and testing involved. The twins gave their informed consent for the study.

Hematology, coagulation, biochemistry and urine analyses produced normal findings in both twins. The levels of hypothalamus hormones (vasopressin and oxytocin) and pituitary gland hormones corticotropin (ACTH), prolac-

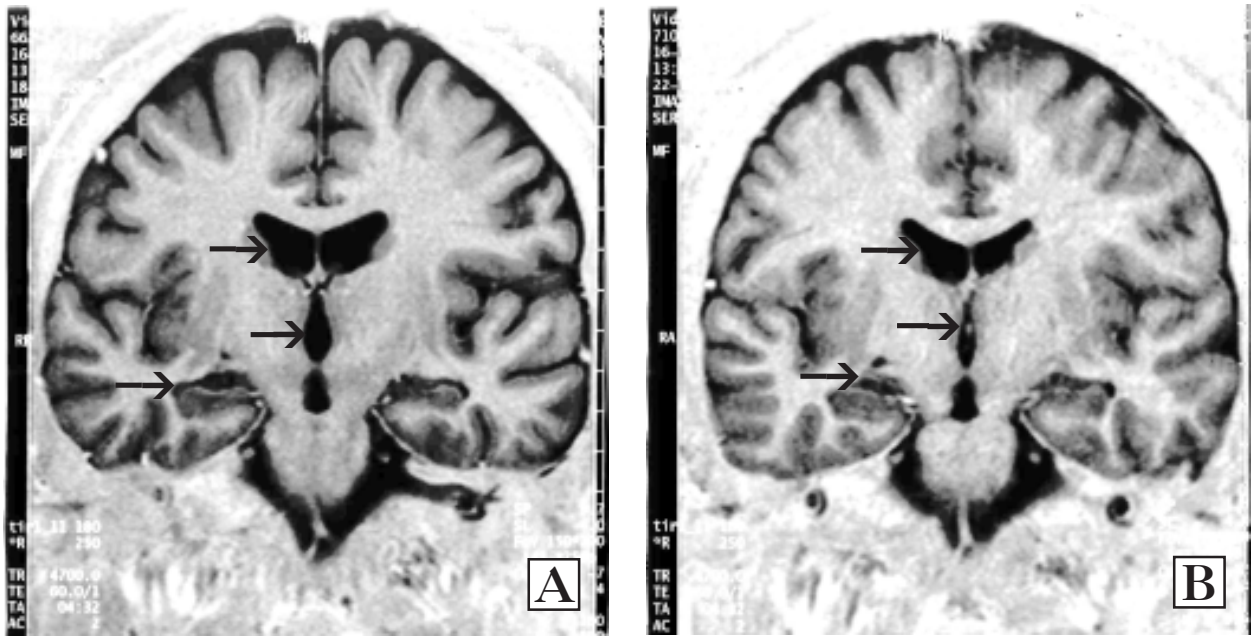

Fig. 1.Magnetic resonance imaging, coronal plane, at the level of hippocampus in the monozygotic twin with (A) and without (B) schizophrenia. Arrows show enlargement of the lateral and third ventricles, smaller hippocampus, and more pronounced parietal and temporal cortical atrophy in the affected twin as compared with the unaffected twin.

tin (PRL), thyrotropin hormone (TSH), luteinizing hormone (LH) and follicle-stimulating hormone (FSH), were within the normal range. Thyroid hormones triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3) and free thyroxine (FT4); adrenal gland hormones cortisol, plasma renin activity and aldosterone; and gonadal hormones testosterone, estrogens and progesterone were normal.

An experienced psychiatrist applied several psychiatric rating scales, i.e. Positive and Negative Symptom Scale for Schizophrenia (PANSS), Hamilton Depression Scale, and Hamilton Anxiety Scale. On the PANSS scale, the schizophrenic twin achieved a total score of 25 *versus* 3 scored by the healthy twin. Psychological assessment was based on the administration of two different questionnaire sets. One set included personality tests such as Minnesota Multiphasic Personality Inventory-201 (MMPI-201), Emotions Profile Index (EPI) and Eysenck Personality Questionnaire (EPQ). The other set included neuropsychological tests such as Bender Gestalt test (BG), Benton Visual Retention test, and Complex Figure Rey Test (CFRT). Personality tests showed increased scores on the paranoid, anxiety and depression MMPI-201 subscales in the schizophrenic twin, whereas in the healthy twin all test variables were normal. The affected twin also showed an increased level of aggression and affect disturbance, along with a decreased level of social functioning. Both twins had high IQ (around 120). On neuropsychological testing, both twins showed visuospatial difficulties, poor attention and vigilance. A neuropsychiatrist also applied a set of tests to assess the 'soft neurologic signs'.

Both twins are right-handed, being clumsy on right- and left-sided motor sequencing tests and fine motor movements. On reproduction drawings, they showed mild distortion or rotation.

Brain MRI (Fig. 1) showed diffuse cortical atrophy of the frontal, parietal and temporal lobes in both twins. This cortical atrophy was more pronounced in the affected twin. MRI in coronal plane showed smaller amygdala and hippocampus, and enlarged lateral third and fourth ventricle in the affected twin as compared with the healthy one. The structures such as medulla oblongata, pons, cerebellum and occipital lobe were of normal morphology in both twins.

Discussion

To the best of our knowledge, only a few reports describing brain morphology in monozygotic twins discordant for schizophrenia based on MRI studies have appeared in the literature to date. These studies pointed to lateral and third ventricular enlargement, frontal lobe atrophy, and smaller hippocampus and amygdala in schizophrenic twins[3-8]. Unaffected twins often have bigger hippocampus and amygdala, and smaller ventricular system in comparison with affected twins[3-8]. Results of these studies are in line with our case report. In contrast to other reports, we found temporal and parietal cortical atrophy in both the schizophrenic and healthy monozygotic twins.

Although our and other studies in monozygotic twins discordant for schizophrenia found affected twins to have smaller hippocampus and amygdala, larger ventricular system and frontal atrophy, the studies comparing brain MRI of unaffected twins or relatives at a high risk of developing schizophrenia showed their MRI findings to bear greater similarity with those of their affected relatives in comparison with normal population[9,10]. These studies have indicated that these morphological changes are associated with familial predisposition to schizophrenia. These changes have also found explanation in the neurodevelopmental model of schizophrenia[2,9,10]. According to this neurodevelopmental model of schizophrenia, the symptoms of schizophrenia are postulated to be a manifestation of disturbed brain development. However, the question remains whether these brain abnormalities are genetically mediated.

Our study also included psychological personality assessment, neuropsychological evaluation and assessment of 'soft' neurologic signs. Personality assessment showed expected changes in the schizophrenic twin and no such changes in the healthy twin, however, neuropsychological evaluation and 'soft' neurologic signs were pathologic in both twins.

It should be noted that the present study suffered from a number of limitations, as it is just a case report, which is also characteristic of other MRI studies in monozygotic twins discordant for schizophrenia, and is thus inadequate for statistical comparison. Additional comparisons at the molecular level, such as serotoninergic or dopaminergic transporter genes, morphological studies, and larger study samples are needed to validate the findings recorded so far.

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Sažetak

SNIMANJE MOZGA MAGNETSKOM REZONANCOM I NEUROPSIHOLOGIJSKO TESTIRANJE U JEDNOJAJČANIH BLIZANACA NESUKLADNIH NA SHIZOFRENIJU

D. Karlović, V. Solter i M. Kalousek

Snimanje mozga magnetskom rezonancom (MR), nedefinirani (*soft*) neurološki znaci, neuropsihologijsko i psihologijsko testiranje osobnosti primijenjeni su na jednom paru jednojajčanih blizanaca starih 25 godina, od kojih jedan boluje od shizofrenije. MR mozga je u oba blizanca pokazao difuznu kortikalnu atrofiju frontalnih, parijetalnih i temporalnih režnjeva. MR u koronalnom presjeku pokazao je smanjene amigdale i hipokampus u bolesnog blizanca. U bolesnog je blizanca nađeno i proširenje trećega i lateralnih ventrikla.

Ključne riječi: *Nenormalnosti mozga; Shizofrenija, patologija; Shizofrenija, genetika; Snimanje magnetskom rezonancom, dijagnostika; Blizanci, jednojajčani*