Association between altered proton magnetic resonance spectroscopy (^{1}H MRS) findings and clinical symptoms of schizophrenia.

Asociación entre las alteraciones en la espectroscopia por resonancia magnética de protón (^{1}H MRS) y los síntomas clínicos de la esquizofrenia.

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SUMMARY

Objective: To assess the metabolic alterations of the thalamus in subjects with schizophrenia compared to healthy subjects and to investigate whether specific schizophrenic symptoms are associated with metabolic alterations measured by ^{1}H MRS. ***Methods:*** This is a case-control study including patients with schizophrenia diagnosed using the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition, DMS-IV and the Operational Criteria Checklist for Psychotic Illness (OPCRIT). Proton magnetic resonance spectroscopy (^{1}H MRS) was used to assess metabolite concentrations (N-acetylaspartate, choline, creatinine, myoionositol and lactacte) in the left and right thalamus of 13 patients with schizophrenia and 13 healthy controls. ***Results:*** In this study, concentrations of specific metabolites in the thalamus, determined by ^{1}H MRS, were similar for individuals with schizophrenia and controls. It was observed that cases with family history of schizophrenia and disorganized speech demonstrated a reduction in the ratio of the metabolites NAA /Cho in the thalamic nuclei on the right side. However, those with organized delusions, hallucinations and non-affective auditory hallucinations had an increase of metabolites on the right side compared to the left thalamus. Decreased thalamic metabolic activity in patients with positive symptoms was observed in contrast with those who had well-organized delusions and auditory non-affective hallucinations, core symptoms of schizophrenia. ***Conclusion:*** A lateralized thalamic involvement was verified, suggesting that organic and genetic factors compromise the right thalamus and that the disorganization associated with delusions and hallucinations compromises the left thalamic nuclei. Further studies to investigate the correlation between symptoms and thalamic dysfunction are warranted. *(Rev Neuropsiquiatr 2011;74:183-190).*

KEY WORDS: schizophrenia, thalamus, magnetic resonance spectroscopy, choline, acetylcholine.

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RESUMEN

Objetivo: Evaluar las alteraciones metabólicas del tálamo en personas con esquizofrenia comparándolas con controles sanos e investigar si los síntomas específicos de la esquizofrenia están vinculados a alteraciones metabólicas medidas por ^{1}H MRS. ***Métodos:*** Se realizó la espectroscopía por resonancia magnética (^{1}H-MRS) para estimar concentraciones de metabolitos (N-acetil- aspartato, colina, creatinina, mioionositol y lactato) en el tálamo izquierdo y derecho de 13 pacientes con esquizofrenia y 13 controles. ***Resultados:*** Las concentraciones de metabolitos específicos en el tálamo fueron iguales para las personas con esquizofrenia y los controles. Se observó que los pacientes con historia familiar de esquizofrenia y aquellos que presentaban lenguaje desorganizado tenían una reducción de los metabolitos NAA/Co en los núcleos talámicos de la derecha. Sin embargo, en aquellos delirios ordenados, alucinaciones no afectivas y alucinaciones auditivas los metabolitos del lado derecho tuvieron cierto aumento con relación a los núcleos talámicos de la izquierda. Se encontró una reducción en la actividad metabólica talámica en los pacientes con síntomas positivos, al contrario de aquellos que presentaron delirios bien ordenados y alucinaciones auditivas no afectivas, los síntomas más nucleares de la esquizofrenia. ***Conclusión:*** Se verificó cierta lateralización del envolvimiento talámico, sugiriendo que los factores orgánicos y los genéticos comprometen el tálamo derecho y que la desorganización asociada a los delirios y alucinaciones compromete los núcleos talámicos a la izquierda. Más estudios son necesarios para investigar la validez de la correlación entre síntomas y disfunción talámica. *(Rev Neuropsiquiatr 2011;74:183-190).*

PALABRAS CLAVE: esquizofrenia, tálamo, espectroscopía por resonancia magnética, colina, acetilcolina.

INTRODUCTION

Schizophrenia is a psychiatric disorder of unknown etiology that has a major psychological and social impact on patients and their families (1). It is characterized by psychotic symptoms, including hallucinations, delusions and thought and speech disorders, emotional and affective disturbances, as well as cognitive and motivational deficits that impair the patient's ability to work and function socially. Schizophrenic symptoms are divided into two large groups, positive and negative symptoms (2). Positive symptoms refer to an exaggeration of normal processes that lead to delusions (for example, delusions of grandeur), whereas negative symptoms (alogia, social withdrawal, avolition, lack of motivation and blunted affect) refer to a decrease in normal processes and are thought to be a direct result of lesions affecting areas of the brain regulating human behavior (2). Schizophrenia is a chronic and recurrent disorder that affects about 1% of the general population. It often occurs in young adults, with variable clinical presentation (1). Early studies investigating structural changes in schizophrenia were able to detect alterations such as enlarged ventricles (3,4) or gray matter volume reduction in the brain of schizophrenic patients (5). However, since this evidence was not consistent and the neurobiological process that produces the symptoms of schizophrenia remains unknown (6) and diagnosis is still based on clinical criteria (7).

More recently, other researchers have shown that changes in the thalamus, an important encephalic subcortical region connecting the limbic system to the prefrontal cortex, with a key role in sensory processing, could explain the symptoms that are typical of schizophrenia, such as hallucinations and/or avolition (8,9).

The significant reduction in the number of nervous cells in the thalamic nucleus reported in several studies might explain abnormalities such as the alteration in synaptic density, volume reduction, and metabolic hypofunction (9,10). Deicken et al. (11) have shown that N-acetylaspartate (NAA, a putative neuronal marker) was reduced in the right and left thalamus of 17 male patients with schizophrenia using in vivo proton magnetic resonance spectroscopic imaging (^{1}H MRSI). Other investigators have shown that ^{1}H MRSI is a useful non-invasive method to study schizophrenia. However, none of these studies have focused on correlating specific clinical symptoms with thalamic alterations and imaging findings. Therefore, the aim of the present study was to assess the metabolic alterations of the thalamus in subjects with schizophrenia compared to healthy subjects and to investigate whether specific schizophrenic symptoms are associated with metabolic alterations measured by ^{1}H MRS.

METHODS

This is a case-control study including patients with schizophrenia diagnosed using the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition, DMS-IV and the Operational Criteria Checklist for Psychotic Illness (OPCRIT). The OPCRIT consists of 90 questions that assess the subject's history, appearance and behavior, speech and form of thought, affect and associated features, abnormal beliefs and ideas, abnormal perceptions, substance abuse or dependence, including a general appraisal by the interviewer.

The method was validated in European Portuguese (12,13) and introduced in Brazil as part of the Brazil/ Portugal International Cooperation Project for the Study of the Molecular Basis of Schizophrenia in the Brazilian and Portuguese Populations (14). The patients were recruited in the community of Passo Fundo, a city with a population of over 180,000 in the South of Brazil, from outpatient clinics at Hospital Psiquiátrico Bezerra de Menezes/Universidade de Passo Fundo, Casa de Saúde São José, and Asilo Nossa Senhora da Luz. They were also referred to the study by clinical psychiatrists.

The inclusion criteria for cases were: older than 18 years of age, not experiencing a psychotic episode, right-handedness, and being literate. Exclusion criteria for this group included having intracranial metallic foreign bodies, alcohol or substance abuse, severe mental, visual or hearing deficit, left-handedness and illiteracy. Exclusion criteria for control subjects were: suffering from any psychiatric disorder, organic disease or substance abuse. Thirty-one individuals were initially enrolled. Of these 18 had a diagnosis of schizophrenia and were undergoing treatment with antipsychotic drugs. Four patients with schizophrenia were not able to undergo the spectroscopy due to involuntary motion or claustrophobia and one was excluded based on diagnostic uncertainty. Therefore, 13 individuals with schizophrenia were studied. The 13 controls were paired to the cases by age, sex, socioeconomic status, and neighborhood of residence. The diagnosis of all the cases included were confirmed using DSM IV criteria and classified according to the International Classification of Diseases (ICD-10). Also, all the patients answered the OPCRIT structured questionnaire, version 3.4, administered by a previously trained psychologist at the Universidade Federal do Rio Grande do Sul psychiatric outpatient clinic. After application of the OPCRIT, cases and controls were reviewed by the team of investigators.

Study protocol

Demographic data were collected by the principal investigator and by a psychologist during the interview with the patient or the person responsible for the patient and the controls. The study was approved by the Ethics Committee and informed consent was obtained from all subjects after the procedures had been fully explained in accordance with the Declaration of Helsinki.

Cases and controls were referred to a local hospital for ^{1}H MRS. Prior to the MRS, subjects answered a questionnaire, in which they were asked whether they had any intracranial metallic foreign body, orthodontic braces, metallic prosthesis, pacemaker or suffered from claustrophobia. The procedure was then explained to them, along with the importance of not moving during the procedure, and the noises the subjects would be hearing during the assessment. No sedation was administered neither to patients nor controls.

The images were acquired with patients in the supine position using Picker brand MRI, model Marconi Medical System, Inc. Eclipse 1.5 T**,** with quadrature head coil. Beams were aligned parallel to the patient's dorsolateral plane, at an angle of 10 degrees in relation to the Frankfort plane. After the patient was positioned, three T_1-weighted images were acquired (relaxation time-TR 1500 ms; echo time -TE 90 ms; matrix 128 X 254; FOV 260 X 260; 16 slices; 15 mm thickness; 1.5 mm spacing), in the sagittal, coronal, and axial planes.

Single voxel spectroscopy was carried out in the three planes, with the voxel located over the right thalamic nuclei, with length of 1.5 cm, width of 1.5 cm, and thickness of 1.5 cm. The voxel matrix consisted of 16 phase-encoding steps in the length and width dimensions, totaling 6 minutes and 30 seconds of acquisition. During acquisition, homogeneity below 7 Hz was ensured, so as to facilitate water suppression. An encephalic magnetic resonance spectroscopy was carried out, obtained in a single session for each test, at the Diagnostic Imaging Department of Hospital São Vicente de Paula, in Passo Fundo, using a Single-Voxel Marconi /Eclipse/ Picker MRI, rated 1.5 Tesla. After the acquisition of pilot images in the axial, coronal and sagittal planes, slices in the semi-axial plane were obtained in T2. These images were used in positioning the location of the spectroscopy's volume of interest.

The voxel was positioned at 10 degrees, parallel to the A-P line, in order to eliminate the susceptibility to artifacts generated by the frontobasal region, measuring

1.5 cm of diameter. Water resonance suppression occurred before the beginning of the spectroscopy sequence. The intensity of the metabolite by the magnetic resonance was automatically and relatively determined in relation to the base line used by the software. The signal of the metabolites was expressed as peaks of NAA and Cr.

The operator selected the area of interest and voxel on the right and left hemisphere thalamus for each control and patient. Each voxel was located entirely within the thalamus to minimize any metabolite contamination from adjacent cerebrospinal fluid or gray and white matter. The voxel selections for each subject were verified by a neuroradiologist and recorded in magnetic resonance photographic images. The voxel was rejected if the height peak was lower than 4 Hz or higher than 10 Hz as of the spectral analysis of the base line; that is, if the difference between the Cr and NAA resonance frequency was lower than 0.95 or higher than 1.05.

No sedation was used in image acquisition. A pilot study was carried out to test the quality of the acquisition and the methodology of data processing. All the tests were carried out between May 24th and July 19th, 2008. Eighteen cases were assessed, including 9 men, 9 women, and 13 controls. Four cases were lost due to technical difficulties during the spectroscopy acquisition, and one additional case was lost during review, remaining thirteen cases for the study.

Two voxels were assessed for each patient: right thalamus and left thalamus. N-acetylaspartate/creatine (NAA/Cr) and N-acetylaspartate/choline (NAA/Cho) ratios were measured.

Table 1. Difference in the ratio of metabolite concentrations in the thamalus in individuals with schizophrenia presenting or not specific symptoms

Metabolites	With	Without	Mean difference (95%CI)	P
Family history	8	5		
NAA/choline R	1.60±0.18	1.84±0.20	-0.24 (-0.48; -0.01)	0.042*
NAA/choline L	1.69±0.24	1.92±0.25	-0.23 (-0.54; 0.08)	0.129
Incoherence	10	3		
NAA/choline R	1.62±0.18	1.92±0.20	-0.30 (-0.56; -0.04)	0.029*
NAA/choline L	1.72±0.24	1.96±0.29	-0.24 (-0.61; 0.12)	0.171
Organized delusions	7	6		
NAA/choline R	1.74±0.24	1.63±0.19	0.11 (-0.16; 0.38)	0.398
NAA/choline L	1.91±0.24	1.62±0.21	0.29 (0.01; 0.56)	0.045*
Widespread delusions	9	4		
NAA/choline R	1.59±0.16	1.91±0.16	-0.32 (-0.53; -0.11)	0.006*
NAA/choline L	1.68±0.22	1.99±0.25	-0.31 (-0.61; -0.01)	0.044*
Delusions/hallucinations	4	9		
NAA/choline R	1.53±0.13	1.76±0.21	-0.23 (-0.49 – 0.02)	0.071
NAA/choline L	1.48±0.11	1.91±0.18	-0.43 (-0.65 – -0.21)	0.001*
Auditory hallucinations	9	4		
NAA/choline R	1.75±0.22	1.55±0.16	0.21 (-0.06; 0.48)	0.114
NAA/choline L	1.88±0.21	1.56±0.26	0.32 (0.03; 0.61)	0.035*

Values expressed as mean ± standard deviation

Table 2. History and symptoms associated with thalamic metabolism

Studied factor	% of difference	Hemisphere	Effect
Family history	13	R	Decrease
Incoherence	16	R	Decrease
Widespread delusions	17	R	Decrease
	16	L	Decrease
Delusions + hallucinations	23	L	Decrease
Well organized delusions	18	L	Increase
Non-affective auditory hallucinations	21	L	Increase

Statistical analysis

Quantitative variables are expressed as means and standard deviation and qualitative variables are expressed as absolute and relative frequencies. The Student's test for independent samples was used to compare mean values of variables with normal distribution. The adopted level of significance was 5% and analyses were carried out using the Statistical Package for the Social Sciences (SPSS), version 15.0.

RESULTS

The mean overall age was 47±20 years. Among the 13 remaining cases, five were male and from the 13 controls, six were male. Therefore, eleven individuals (42.3%) were males. No statistically significant differences were observed between cases and controls regarding metabolite concentrations.

However, as shown in Table 1, a significant difference was observed between schizophrenia symptoms and metabolite concentrations in the thalamus, for NAA/choline ratio in patients with vs. without a family history of schizophrenia (P=0.042); patients with incoherent speech and thought vs. those without (P=0.029); and patients with well organized delusions for at least one month vs. those without well organized delusions or with delusions for less than one month (p = 0.045).

In addition, patients with widespread delusions for at least one month presented a significant lower NAA/choline ratio in the right (P=0.006) and left (P=0.044) thalamic nuclei than those who did not suffer from widespread delusions, or those who did so for less than one month. Patients with widespread delusions and hallucinations for at least one month presented a lower NAA/choline ratio in the left thalamic nucleus (P=0.001) than those who did not suffer from delusions and hallucinations, or those who did so for less than one month. Patients who presented other non-affective auditory hallucinations presented a significantly higher NAA/choline ratio in the left thalamic nucleus than those who did not (P=0.035).

Table 2 shows the type of metabolic change associated with each schizophrenia symptom presenting a statistically significant difference vs. the absence of the symptom, as well as the percentage difference in metabolic activity in the affected hemisphere. Except for well-organized delusions and non-affective auditory hallucinations, a decrease in metabolic activity was associated with all other symptoms.

DISCUSSION

In the present study, the concentrations of specific metabolites in the thalamus, determined by ^{1}H MRS, were similar for individuals with schizophrenia and healthy controls. However, differences were observed when patients with schizophrenia with and without specific symptoms were compared. This was not found in other studies probably due to the patient positioning, voxel size, software employed for analysis, and differences in patient sample.

It seems that in schizophrenia, either the concentration of NAA is low or that of choline is high, which translates into a degradation of the cell membrane (15). Low NAA could also be due to the demyelinization of neuron terminal zones, or gliosis, or to disorders of

phospholipid metabolism (16). This suggests a dysfunction preventing the thalamus from functioning as a sensory filter for excess stimuli. The overload imposed on the prefrontal cortex would cause executive dysfunction (negative symptoms). Alterations in sensory filtering would also originate cognitive and sensory perception dysfunctions (positive symptoms such as hallucinations, delusions and psychomotor agitation). Thalamic alterations would thus explain, at least in part, the disattention process which occurs in patients with schizophrenia, since that region is closely related to the filtering of irrelevant stimuli (17).

One of the objectives of this study was to investigate the existence of differences in thalamic dysfunction relating to specific symptoms. We observed that the patients with a family history of schizophrenia presented a reduction in NAA/Cho ratio in the right thalamic nuclei. Patients with incoherence (disorganized speech) also showed a reduction in metabolite concentrations in the right hemisphere. These findings could support the organogenetic basis of schizophrenia hypothesis, which may in turn explain the thalamic dysfunction in this disease. Csernansky et al. (18) have established that there is no correlation between the severity of symptoms and thalamic alterations; rather, the type of symptom seems to be more important.

Patients with organized delusions, non-affective hallucinations and auditory hallucinations had an increased NAA/Cho ratio in the left thalamic nuclei. When delusions and hallucinations were specifically studied, a reduction in NAA/Cho in the left side was observed, indicating more acute dysfunction; in widespread delusions, evidence was found of bilateral thalamic alterations. Although these findings must be tested in larger samples, they suggest an asymmetrical dysfunction of thalamic nuclei in schizophrenia. The NAA/Cho ratio was observed to be decreased in the left thalamus, probably due to a reduction in NAA and/or an increase in choline. This is partially consistent with the findings of Ferreira (19) and with studies reporting low concentrations of absolute NAA in schizophrenia. The present evidence suggests aspects of functional lateralization which could be lost or reversed in schizophrenia and support the observations of previous studies (18, 20, 21). Pliska and Weinberg (17) have also reported changes in the left thalamus.

The cases in which a bilateral reduction of the NAA/Cho ratio was observed could be reflecting an association of two basic factors: genetic (low-resistance brain circuits, low ability to establish circuit inhibition-deactivation), which under the effect of environmental or internal/hormonal stimuli (such as cortisol or testosterone) become unbalanced and lose their ability for self-regulation, thus resulting in an expansion of the dysregulation. This hypothesis is consistent with studies on the cortical-striatal-thalamic circuit (22).

We observed decreased thalamic metabolic activity in patients with positive symptoms. Three explanations could be considered: a) the decreased activity reflects the brain dysfunction associated with psychotic symptoms; b) the reduction reflects a cerebral reaction of adaptation and control of the brain dysfunction of psychosis; or c) the decrease reflects the effect of the medication used to control the psychosis. Curiously, an increase in metabolism was observed in relation to well-organized delusions and non-affective auditory hallucinations, precisely the most nuclear symptoms of schizophrenia.

New research describes the possibility of non-reciprocal connections between the thalamus and the brain cortex. There seems to be convergence between cortical regions in the thalamus as well as in the striatum nucleus (22,23). This aspect deserves further research.

The limitations of this study must be discussed. First, the sample size was small. According to the meta-analysis carried out by Steen et al (24), reliable results would require at least 39 cases and 39 controls. Nevertheless, we believe that our findings are consistent with those of previous reports and that the inclusion of more patients would in fact reinforce our observations. The technical impossibility of isolating and studying the sub-regions of the thalamus is another constraining factor (8). In this study, the voxel was placed so as to contain only the thalamus, leaving out the cerebrospinal fluid. The use of the NAA/Cho ratio, despite being more reliable than absolute measurements, might be a limitation for the determination of absolute concentrations (11,19,25,26).

It should be noted that, considering the fact that as the diagnosis of schizophrenia is still based on clinical symptoms it is thus subject to diagnostic bias, therefore the use of standardized classification systems such as the Operational Criteria Checklist for Psychotic Illness (OPCRIT) was a positive aspect. This type of system provides computer-defined algorithms and operational criteria to aid in the clinical diagnosis and provide guidance for evidence-based decision-making (27).

In summary, although no significant alterations in metabolite concentration were observed when comparing cases and controls, differences were found between patients with schizophrenia presenting or not specific symptoms. A lateralization thalamic involvement was verified, suggesting that organic and genetic factors compromise the right thalamus and that the disorganization associated with delusions and hallucinations compromises the left thalamus nuclei, whereas some situations, such as in widespread delusions, seem to result in thalamic dysfunction. Further studies to investigate the correlation between symptoms and thalamic dysfunction are warranted.

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