Archives of Psychiatry and Psychotherapy
Volume 7, Issue 4, December 2005
pages 17–25

Clinical and neuropsychological correlates of proton magnetic resonance spectroscopy detected metabolites in brains of first-episode and chronic schizophrenic patients

Agata Szulc [1], Beata Galińska [1], Eugeniusz Tarasów [2], Jerzy Walecki [2], Wojciech Dzienis [2], Bożena Kubas [2], Andrzej Czernikiewicz [1].

[1] Psychiatry Departament, Medical Academy, Białystok
Director: dr hab. Andrzej Czernikiewicz
[2] Radiology Department Medical Academy, Białystok
Director: prof. dr hab. Jerzy Walecki

Summary

Aim: This study examined 1H MRS detected metabolite levels (in left frontal, temporal lobes and thalamus) and clinical and cognitive features of patients with first-episode and chronic schizophrenia.

Material and method: We studied 31 first-episode patients (group 1) and 17 chronic patients (group 2) with an ICD-10 diagnosis of schizophrenia (and 13 healthy subjects). Patients were also assessed by the means of PANSS, CGI, Calgary scales and WCST, TMT, Stroop tests.

Results: We did not observe any statistically significant differences in metabolite levels between group 1 and 2. We observed only a trend toward a higher Cho level in temporal lobe in group 2 and lower NAA level in group 1. When comparing with the control group, we observed a significantly higher Cho level in the frontal lobe (group 1, 2) ($p<0.05$). We also observed a trend towards lower NAA levels in the frontal lobe (group 1, 2), and lower NAA level in the temporal lobe (group 1). Patients with chronic schizophrenia performed significantly worse in WCST, TMT and Stroop tests ($p<0.05$).

Conclusion: These results suggest that abnormalities in metabolite levels in frontal and temporal lobes are present at the onset of disease and don't progress over time. The cognitive dysfunction is more prominent in chronic patients.

Key words: Schizophrenia, proton magnetic resonance spectroscopy, cognitive functions

Introduction

Magnetic Resonance Spectroscopy (MRS) is a method which allows the detection of metabolic changes in vivo. The method makes it possible to study in a non-invasive manner, the metabolism of regular brain tissue cells and cells affected by various morbid states as hypoxia, infarct, neoplasm, degeneration, multiple sclerosis, dementia and epileptogenic focus [1].

In the studies on schizophrenia, two types of spectroscopy were applied the most often: phosphorus compounds spectroscopy (31P) and proton spectroscopy (1H). In proton spectroscopy (1H MRS) the signals deriving from: N-acetylaspartate (NAA), Creatine and Phosphocreatine (Cr+PCr), compounds including Choline group (Cho), Myoinositol (mI), Glutamine, and Glutamates, can be seen. Creatine (Cr) is recognised as an indicator of the energetic state of the brain. A level of Cr concentration, because of its relative stability, is used to measure its proportion to other metabolites. Choline (Cho) is considered as an indicator of the products of myelin degradation. N-acetyloaspartate (NAA) participates, inter alia, in neuronal peptides synthesis, neurotransmitter metabolism and it is regarded as an indicator of neuronal function. Myoinositol pertains in phospholipids and is found only in astrocytes. Glx is a common signal for glucose, GABA (gamma-Aminobutyric Acid), glutamine, and glutamic acid. Proportions of the mentioned metabolites are estimated in relation to creatine or water (e.g. NAA/Cr or NAA/H2O). Phosphoric spectroscopy allows evaluating the brain membrane phospholipids and energetic metabolism of a cell [2].

Bertolino and Weinberger in the paper from 1999 [3] surveyed the studies of 1H MRS in schizophrenia and concluded that in the majority of studies carried out on patients with schizophrenia, a lower NAA level in the area of the hypocampus and temporal lobe has been detected. Many authors observed a decrease of the NAA level in the prefrontal dorsolateral cortex of the frontal lobe. On the basis of the review of papers referring to studies of 31 P MRS and 1 H MRS in schizophrenia, Kegeles and coll. [4] concluded that frontal lobes are the areas where a decrease of the PME (phosphomonoesters) signal and an increase of PDE (phosphodiesters) signal were detected the most often. Whereas in temporal lobes, lower NAA signal was detected the most often. Studies of 1H MRS, which demonstrated changes in the metabolism of frontal, temporal, hippocampus area, and basal ganglia are coherent with the reports about volumetric reduction and disturbed functional activity in those brain areas [5, 6]. So far there are occasional reports in which MRS results are coherent with the clinical picture and cognitive function disturbances which are one of the main features of schizophrenia, in the literature [7, 8, 9].

The aim of this study was an estimation of the relationship of metabolic changes in the brain with cognitive function disorders and the clinical picture in the first-episode and chronic schizophrenia.

Material and method

Two groups of patients with a diagnosis of schizophrenia according to ICD-10, hospitalised in the Psychiatric Clinic AMB and SPP health care centre in Choroszcz, were included in the study. Group 1; 31 patients with a first episode of the illness, in the age 18-40 y.o. Group 2; 17 patients having chronic schizophrenia, i.e. suffering for 5-10 years, in the age 18-45 y.o. Group 1 included 21 (67.7%) males and 10 (31.3%) females, and Group 2 – 12 (70.5%) males and 5 (29.5%) females. The average age in Group 1 was 22.55±3.5 y.o., the average age in Group 2 was 33.59±7.40 y.o. All of the patients were receiving neuroleptics during the course of the study. The criteria

excluding patients from the study were the detection of organic CNS damage, addiction to alcohol and other psychoactive substances and contraindications for MRI performance. Psychical state was assessed using the following scales: PANSS (scale for assessment of positive and negative symptoms of schizophrenia) [10]; Calgary scale (scale for assessment of depression appearance in schizophrenia) [11]; CGI scale (general clinical assessment scale).

Neuropsychological assessment included the following tests:

1. Wisconsin Card Sorting Test (WCST) – the test serves the assessment of operational memory and executive functions, and is recognised as one of the most important tools of frontal lobe damage assessment. It is an extraordinarily sensitive method of detection of perseveration. Schizophrenic patients have tendencies towards perseveration and they do not modify their strategy of activity when reaction criteria change during task performance [12].
2. Stroop test – the test assesses verbal skills, operational memory, and executive functions.
3. Dot connecting test, part A and B (TMT) – examines the visual-dimensional operational memory and the capacity for switching to new criteria after they have learned one scheme of reaction. The test examines also visual-motor co-ordination [13].

MRI and MRS examination

Every patient had an MRI scan and MR proton spectroscopy. The scans were performed using a MR tomography scanner equipped with a magnet having 1.5 T field intensity. Voxels (the areas of interest) with the dimension 2 x 2 x 2 cm were localised in the area of frontal, temporal lobe, and in the thalamus on the left side. Most of the neuro-imaging examinations of the brain in schizophrenia, were performed in the left hemisphere, as a dominating one (all of those examined were right-handed). Resonance spectrums were registered according to the following parameters: sequence PRESS with TE=35 ms, TR=1500 ms, number of repetitions =192. The water signal was suppressed by the MOIST sequence. Preparation of the spectrum was performed on the basis of an automatic procedure supplied by the Picker company. In the final spectrum, the content of metabolites, on the basis of their proportion to creatine and the unsuppressed water signal, was evaluated. In this paper we show the results regarding the NAA and Cho (elaboration of the other substances is in process, e.g. Glx). In the analysis of the results of proton spectroscopy a control group, consisting of 13 healthy persons (7 men and 6 women, average age – 24.23±1.36 y.o.), was used.

For a statistical elaboration of the results, according to the character of the studied variables, the ANOVA test and a post hoc NIR test to verify more complex hypotheses were applied, and the Pearson correlation rates have been counted to define relations between variables. For counting, the Statistica 5.5 PL software was applied.

Results

The clinical features of the both groups are shown in table 1. The group of patients suffering from chronic schizophrenia was characterised by higher results in the PANSS

scale, there were no differences regarding the CGI and Calgary scales. In the group of chronic schizophrenia sufferers the average period of the illness was 9.33±4.87 years, and the number of hospitalisations was 7.87±5.84. The level of education (in years) in the group of patients with the first episode amounted to 13.3±2.2, and in the group of patients with chronic schizophrenia – 12.14±0.53.

Table 1

Clinical Characteristics of the studied groups.

	Group 1(first episode)		Group 2 (chronic schizophrenia)	
	Mean	SD	Mean	SD
CGI	4.84	1.00	4.73	0.46
PANSS-Complete	79.71	13.43	88.60	10.03
PANSS-Positive	17.61	4.34	16.20	3.99
PANSS-Negative	22.03	6.53	24.87	2.80
PANSS-General	39.74	6.67	47.53	6.40
Calgary scale	7.06	5.34	7.53	4.91

Proton spectroscopy results

The results of the proton spectroscopy were obtained in 31 patients with the first episode of illness and in 17 patients with chronic schizophrenia (picture 4). No significant differences in the studied areas between the two groups of patients regarding the NAA and choline spectrums have been observed. However, a trend towards an increased level of choline (Cho/Cr) in the left temporal lobe in the group of chronically ill patients and in the group of patients with the first episode, as well as a trend towards a lower level of NAA (NAA/Cr and NAA/H2O) in the left temporal lobe, have been found. After the analysis of the three groups, including the control group, we found that regarding choline (Cho/Cr and Cho/H2O) in the left frontal lobe, the results in both groups of the ill were higher than in the control group ($p<0.05$). We also observed a trend towards a lower level of NAA (NAA/Cr and NAA/H2O) in the left frontal lobe – in both groups of the ill in comparison to the control group. In this analysis as well, a trend towards a lower level of NAA (NAA/Cr and NAA/H2O) in the temporal lobe in the group of patients with the first episode, can be seen. We also obtained higher results regarding the choline level (Cho/Cr) in the thalamus in both groups of the ill (differences are not statistically significant). The detailed results are shown in table 2.

Results of the neuropsychological tests

WCST test was performed in 30 persons from the group of patients with first episode and 15 persons from the group of suffering chronically and TMT and Stroop tests were performed in 15 persons in both groups. The detailed results are shown in table 3. In the group of patients having chronic schizophrenia we noted more mistakes in

the WCTS test, e.g. more perseveration mistakes and perseveration answers, and also less completed categories. As far as the TMT A and B tests and also the Stroop test, chronic schizophrenia sufferers required more time to perform them (tab. 3).

Table 2

Results of magnetic resonance proton spectroscopy.

Metabolite	Group 1 (first episode)		Group 2 (chronic schizophrenia)		Control Group		p
	mean	SD	mean	SD	mean	SD	
NAA/Cr C	1.79	0.38	1.81	0.23	2.02	0.38	Ns
NAA/Cr S	1.66	0.29	1.83	0.30	1.83	0.30	Ns
NAA/Cr W	1.92	0.29	1.92	0.37	1.90	0.22	Ns
NAA/H2O C	0.46	0.08	0.46	0.12	0.51	0.04	Ns
NAA/H2O S	0.41	0.09	0.45	0.11	0.45	0.07	Ns
NAA/H2O W	0.54	0.06	0.56	0.05	0.54	0.04	Ns
Cho/Cr C	0.98[1]	0.11	0.96[2]	0.19	0.82[12]	0.09	<0.05
Cho/Cr S	0.97	0.14	1.06	0.27	0.97	0.14	Ns
Cho/Cr W	0.87	0.13	0.87	0.16	0.79	0.12	Ns
Cho/H2O C	0.26[1]	0.04	0.24	0.06	0.21[1]	0.04	<0.05
Cho/H2O S	0.24	0.05	0.26	0.07	0.24	0.05	Ns
Cho/H2O W	0.24	0.05	0.26	0.02	0.23	0.04	Ns

C – left frontal lobe, S – left temporal lobe, W – left side thalamus, Ns – statistically insignificant
[1] – statistically significant difference, group 1 vs. control group, [2] – statistically significant difference, group 2 vs control group

Table 3

Results of neuropsychological tests

Results	Group 1 (first episode)		Group 2 (chronic schizophrenia)		p
	mean	SD	mean	SD	
WCST: TE	40.13	25.83	61.15	23.40	<0.05
WCST: PR	21.00	11.20	44.15	28.94	<0.05
WCST: PE	18.97	10.17	37.46	21.39	<0.05
WCST: NPE	21.17	19.26	23.69	18.01	Ns
WCST: CC	4.40	2.16	2.15	2.03	<0.05
TMT A (seconds)	34.08	12.35	75.47	29.67	<0.05
TMT B (seconds)	69.08	27.06	149.17	64.13	<0.05
Stroop 1 (seconds)	23.54	3.78	29.40	5.90	<0.05
Stroop 2 (seconds)	61.27	16.90	78.71	24.43	Ns

TE – number of mistakes, PR – number of perseveration answers, PE – number of perseveration mistakes, NPE – number of non-perseveration mistakes, CC – number of completed categories.

The correlation between spectroscopy results, clinical data and neuropsychological tests in the whole group of patients suffering from schizophrenia, i.e. group of patients with the first episode and chronically ill together has been analysed. Correlation between spectroscopy results and age, duration of hospitalisation and the number of hospitalisations, and also the results of CGI and Calgary scales has not been detected. Pertaining to the PANSS scale, the following positive correlations have been noted: PANSS – negative scale, general scale, total scale and choline level in thalamus ($p<0.05$). According to the WCST test the following positive correlations were found: the number of perseveration mistakes and the choline level in the temporal lobe and NAA level in thalamus, the number of perseverative answers and NAA level in the thalamus ($p<0.05$).

Discussion

The results obtained in the study confirm to a large extent the data from professional literature referring mostly to a lowered NAA and an elevated Cho level in the brains of schizophrenia sufferers. The differences were the most significant regarding choline level in the left frontal lobe in both groups of schizophrenia sufferers in comparison to the control group. Differences in NAA levels in frontal and temporal lobes were statistically insignificant. Although both groups of the ill did not differ significantly from each other, we observed a trend towards an increased temporal lobe Cho level in the group of chronically ill and a reduced NAA level in the group of patients with first-episode schizophrenia. In our previous research [14] these differences were more emphasised, probably because at the time we analysed a group of older subjects (approx. 45 y.o.) and also those suffering for a longer period (approx. 15 years). Perhaps the age influence has been more apparent rather than one of the illness processes in particular. In the current study, the patients with chronic schizophrenia are younger but with a long course of illness. Moreover, no correlations of metabolite levels with age or illness duration have been found. The obtained results referring to metabolite levels may give evidence to the existence of changes, especially those regarding choline in the frontal lobe, already at the beginning of the illness. On the other hand, the lacking of significant differences between both groups, may be evidence that the described changes do not undergo further progressiveness along with the duration of the illness. It is also not unlikely that chronic neuroleptic treatment may have any result on the metabolite levels. In the previous study, in which we examined 16 patients with the first episode of schizophrenia, we detected a significantly increased choline level and a decreased NAA level in the left frontal lobe in this group of patients in comparison to a control group. In the temporal lobe a trend towards a reduction of the NAA level has been observed, something we also confirmed in the presented study [15]. Deicken and coll. [16] detected a reduced NAA level in the left frontal lobes of patients with the diagnosis of schizophrenia, and Cecil and coll. [5] found a decreased NAA levels in a group of patients with the first episode of schizophrenia, both in the frontal and temporal lobes and a slightly increased choline level in frontal and decreased in the temporal lobes.

One of the main questions was to verify the argument that changes in the CNS and cognitive function disturbances exist in a high intensity already from the beginning of the disease and during the chronic period. Cognitive deterioration in the course of schizophrenia seems to be particularly relevant to the period directly after the first psychotic episode, and does not deepen in a later period (so called 'static encephalopathy' according to Goldberg) [17]. In our study patients suffering chronically from schizophrenia had worse results in neuropsychological tests. It may give evidence to the progression of these changes along with the duration of the illness. Possibly, the performance of these tests was influenced by the prolonged neuroleptic treatment. Furthermore, chronically ill patients were characterised by higher results in the PANSS scale (overall and general) which could also have an influence on the differences noted. It has not been confirmed unequivocally so far whether cognitive disturbances in schizophrenia are constant and do not develop in the course of the illness or that we are dealing with a kind of progressive 'dementia'. Previous studies provide more evidence speaking in advocacy of the first theory. Hoff and coll. [18] stated that patients with schizophrenia are characterized by significant cognitive dysfunction, which is stable during the first five years of disease. Older patients with schizophrenia do not seem to be more intellectually disturbed than the young, if the influence of the ageing process is considered [19]. Frith and coll. in turn observed the deterioration of cognitive functions during the first five years of the disease and found a subsequent stabilisation of those changes.

Considering the correlation of metabolite levels with clinical data and results of neuropsychological tests, it actually is still difficult to interpret. Attempts to define the correlation between the symptoms of schizophrenia, including negative and positive symptoms, and particular morphologic abnormalities have been undertaken before, but the results are uncertain [20, 21, 22]. The PANSS results obtained by us correlated with the choline level in the thalamus. This could confirm that this structure is involved in the pathogenesis of the symptoms of schizophrenia. On the other hand, Callicott and coll. found a negative correlation between the NAA level in the frontal lobe and negative symptoms [8]. Considering results of the WCTS test, the higher number of mistakes correlated with choline and NAA levels in the thalamus and temporal lobe. Perhaps the abnormalities in these structures influencing the clinical picture of the illness, indirectly influence the test results. In the international literature there are sporadic reports referring to the subject. Hoff and coll. [18] have not found any correlation between cognitive disorders and the results of the MRI studies. DeLisi and coll. [23] found only a partial correlation between the results of tests referring to verbal memory and the extension of the peri-hypocampus area. Bertolino and coll. [7] showed that the results regarding N-acetylaspartate (NAA) obtained by MR proton spectroscopy method highly correlated with an activation of the extended areas of operational memory (dorsolateral prefrontal cortex, temporal and lower parietal cortex) during the performance of memory tests. Ohrmann and coll. [9] found a correlation between the results of the auditory word learning test and NAA and GLX metabolite levels in frontal cortex of patients suffering from schizophrenia.

Conclusions

The present study has an introductory character. Abnormalities in choline and NAA levels in the frontal lobe may prove a reduction of neurones in the area, which is present at the beginning of the illness and does not undergo any changes along with the illness progression. Regarding cognitive functions, in the group of patients chronically suffering from schizophrenia, worse performance of neuropsychological tests is observed. This may give evidence on the progression of symptoms in this area. Correlations of metabolite levels require further analyses and prospective studies.

References

1. Kuliszkiewicz-Janus M. *Spektroskopia magnetycznego rezonansu jądrowego (Magnetic Resonance Spectroscopy – MRS) w badaniu fizjologii i patologii mózgu.* Post. Med. Klin. Dośw. 1993; 2: 167–177.
2. Urbanik A, Sobiecka B, Kozub J, Chrzan R, Jeleńska I. *Widmo badania RM mózgowia w technice spektroskopii protonowej metodą pojedynczego, zlokalizowanego voxela.* Pol. Przegl. Rad. 2001; 66(1): 7–11.
3. Bertolino A, Weinberger DR. *Proton magnetic resonance spectroscopy in schizophrenia.* Eur. J. Radiol. 1999; 30: 132–141.
4. Kegeles LS, Humaran TJ, Mann JJ. *In vivo neurochemistry of the brain in schizophrenia as revealed by magnetic resonance spectroscopy*. Biol. Psychiatry. 1998; 44: 382–398.
5. Cecil KM, Lenkinski RE, Gur RE, Gur RC. *Proton magnetic resonance spectroscopy in the frontal lobe of neuroleptic naïve patients with schizophrenia*. Neuropsychopharmacology. 1999; 20: 131–140.
6. Galińska B, Szulc A, Walecki J, Kubas B, Tarasów E. *Postępy w neuroobrazowaniu schizofrenii: spektroskopia rezonansu magnetycznego*. Pol. Merk. Lek., in press.
7. Bertolino A, Esposito G, Callicot JH, Mattay VS, Van Horn JD, Frank JA, Berman KF, Weinberger DR. *Specific relationship between prefrontal neuronal N-Acetylaspartate and activation of the working memory cortical network in schizophrenia*. Am. J. Psychiatry. 2000; 157: 26–33.
8. Callicott JH, Bertolino A, Egan MF, Mattay VS, Langheim FJP, Weinberger DR. *Selective Relationship Between Prefrontal N-Acetylaspartate Measures and Negative Symptoms in Schizophrenia*. Am. J. Psychiatry. 2000; 157: 1646–1651.
9. Ohrmann P, Suslow T, Siegmund A, Kersting A, Spitzberg M, Fiebich M, Heindel W, Arolt V, Pfleiderer B. *Neuronal dysfunction of the left frontal lobe correlates with verbal learning in schizophrenic patients*. Eur. Arch. Psychiatry Clin. Neurosci. 2002; 252, Suppl. 1: 62.
10. Kay SR, Fiszbein A, Opler LA. *The Positive and Negative Syndrom Scale (PANSS) for Schizophrenia*. Schizophr. Bull. 1987; 13: 261–276.
11. Addington D, Addington J, Maticka-Tyndale E. *Assessing depression in schizophrenia: The Calgary Depression Scale*. Br. J. Psychiatry. 1993; 163, suppl. 22: 39–44.
12. Heaton RK. *Wisconsin Card Sorting Test: Computer Version 2 Research Edition*, by Psychological Assesment Resources, Inc. 1990, 1993.
13. Borkowska A. *Współczesne metody badań neuropsychologicznych w zaburzeniach psychicznych.* Post. Psychiatr. Neurol. 1999; 8: 153–164.
14. Szulc A, Tarasów E, Galińska B, Kubas B, Dzienis W, Czernikiewicz A, Walecki J. *The effect*

of duration of illness on metabolic abnormalities in schizophrenia by in vivo proton magnetic resonance spectroscopy. European Radiology. 2003, Suppl. 1, 524.

15. Galińska B, Szulc A, Tarasów E, Kubas B, Czernikiewicz A, Walecki J. *Spektroskopia protonowa MR wybranych obszarów mózgowia w grupie pacjentów z pierwszym epizodem schizofrenii*. Badania nad schizofrenią 2002, in press.
16. Deicken RF, Zhou L, Corwin F, Vinogradov S, Weiner MW. *Decreased left frontal lobe N-Acetylaspartate in schizophrenia*. Am J Psychiatry. 1997; 154: 688–690.
17. Goldberg T, Hyde T, Kleinman J, Weinberger D. *Course of schizophrenia: Neuropsychological evidence for a static encephalopathy*. Schizophr. Bull. 1993; 19: 797–804.
18. Hoff AL, Sakuma M, Wieneke M, Horon R, Kushner M, Delisi LE. *Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia*. Am. J. Psychiatry 1999; 156: 1336–1342.
19. Calev A. *Neuropsychology of schizophrenia and related disorders. In: Calev A. ed. Assessment of neuropsychological functions in psychiatric disorders*. New York: American Psychiatric Press, Inc.; 1999.
20. Anczewska M, Tarczyńska K, Węgrzyn J. *Badania obrazowe mózgu a schizofrenia*. Post. Psychiatr. Neurol. 1999; 8: 327–340.
21. Szulc A. *Diagnostyka obrazowa mózgu w schizofrenii – ze szczególnym uwzględnieniem Tomografii Komputerowej*. Psychiatr. Pol. 1994; 28: 145–156.
22. Walczewski K, Cechnicki A, Matkowski J, Kleinrok K, Herman I, Podsiadło-Kleinrok B. *Związki między anomaliami strukturalnymi mózgu a obrazem psychopatologicznym u chorych na schizofrenię*. Psychiatr. Pol. 2001; 35: 33–46.
23. DeLisi LE, Hoff A, Schwartz JE, Shields GW, Halthore SN, Gupta SM, Henn FA, Anand A.K. *Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitive magnetic resonance imaging study*. Biol. Psychiatry.1999; 29: 159–175.

Autor's address:
Agata Schulz
Psychiatry Departament AMB
16-070 Choroszcz k. Białegostoku, Poland.