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Measurement of glycine in a brain and brain tumors by means of 1H MRS

Barbara Bobek-Billewicz[1], Anna Hebda[1], Gabriela Stasik-Pres[1], Krzysztof Majchrzak[2], Elżbieta Żmuda[3], Agnieszka Trojanowska[4]

[1]Radiodiagnostic Department, Comprehensive Cancer Centre Maria Sklodowska-Curie Memorial Institute Branch Gliwice, Poland,
[2]Department of Neurosurgery, Medical University of Silesia in Katowice, Sosnowiec, Poland, [3]Department of Radiology, Oncology Centre in Bydgoszcz, Poland, [4]Department of Radiology, Medical University of Lublin, Poland

Abstract

Aim: *Evaluation of a peak at 3.55 ppm in a long echo time (TE) recognized as glycine (Gly) in the WHO grade II gliomas and central neurocytomas by means of 1H MRS.*
Material and methods: *Retrospective analysis of 19 patients with histopathologically confirmed WHO grade II glioma and 2 patients with central neurocytoma was conducted. 1H MRS (TE = 135 ms and TE = 144 ms) was performed with 1.5 T and 3.0 T scanners. Gly/Cr, Gly/Cho and Gly/NAA ratios were compared between the analysed groups. Additional analysis of a brain of 61 healthy volunteers was conducted.*
Results: *Glycine was distinguished in 12 out of 19 (63%) WHO grade II gliomas. Among those 12 WHO grade II gliomas only in 26% of a spectra Gly was recognized. In both central neurocytomas Gly was distinguished and in 43% of the spectra Gly was recognized. The ratio of Gly/Cr in central neurocytomas was higher than in WHO grade II gliomas (mean$_{CNC}$ 0.62 ± 0.18 vs. mean$_{WHO\,II}$ 0.37 ± 0.10; p < 0.001) but the ratio of Gly/Cho was lower (mean$_{CNC}$ 0.18 ± 0.04 vs. mean$_{WHO\,II}$ 0.24 ± 0.07; p < 0.001). There was no difference between analysed groups in terms of Gly/NAA ratio (mean$_{CNC}$ 0.36 ± 0.09 vs. mean$_{WHO\,II}$ 0.36 ± 0.14; p = NS). Only in 0.3% of the spectra of normal brain Gly was distinguished.*
Conclusions: *Glycine is found in WHO II grade gliomas as well as in central neurocytomas, but only in a part of a tumor volume. It is necessary to perform 1H MRS of the whole tumor volume to confirm/exclude the presence of glycine. Glycine in a normal brain can not be identified by means of conventional 1H MRS performed by means of 1.5 T or 3.0 T scanners.*

Key words: *glycine, long echo time, central neurocytoma, WHO grade II glioma.*

Introduction

Proton magnetic resonance spectroscopy (1H MRS) is mainly used in diagnostic of brain and prostate diseases [6,13,26,35], but in recent years there have been attempts of using this method in diagnostic of breast [2] and other organs diseases.

The application of 1H MRS has been used for brain tumor differentiation from other diseases, determination of malignancy or histopathologic

Communicating author:

lek. Gabriela Stasik-Pres, Comprehensive Cancer Centre Maria Sklodowska-Curie Memorial Institute Branch Gliwice, Wybrzeże Armii Krajowej Str 15, 44-101 Gliwice, Poland, phone 693 542 283, e-mail: gabastasik@poczta.onet.pl

types and metabolite profile of neoplastic tissue [3,9,16,18,19,30,31,34,39].

Glycine is an amino acid synthesized from serine in the synaptic vesicles which acts as a neuromodulator or antioxidant. It is distributed throughout different parts of central nervous system [11,23,39]. Glycine has two methylene-protons ($-CH_2$) gropus that co-resonate at 3.55 ppm as a single peak [7,8,11,14,30,37]. It should be noted that at 3.52-3.57 ppm in short echo time Gly overlaps with myo-inositol (mI) [12,30,37]. On the other hand in long echo time (TE 100-170 ms) mI has short T2 relaxation time so its contribution to magnetic resonance spectrum is reduced considerably. Therefore in long echo time peak at 3.55-3.57 ppm is assigned to Gly rather than to mI [11,14,41].

Gly concentration in the normal brain range from 0.4 to 1.0 mmol/kg_{ww} [8,30]. The concentration of Gly is elevated in patients with hyperglycinemia and tumors such as glioblastoma multiforme, medulloblastoma, ependymoma and central neurocytoma [8,14,37,41]. It has been also found in other pathologies of a central nervous system like stroke, adrenoleukodystrophia or hamartoma [34]. On the contrary it has been recomended that Gly presence is a typical feature of CNC [5,16,14,15,40,41], though its absence do not exclude CNC [5,15,18,19].

CNC consist of uniform round cells with neuronal differentiation comparable with oligodendrocytes [24,27,39,41]. Calcifications, necrosis and tiny cysts may occur in both of the tumors [14,24,26,32,39]. Because of great morphological similarity to oligodendroglioma or ependymoma it makes difficult to differentiate these tumors and extraventicular neurocytoma in imaging and histopathologic examinations [24,27,32,39,40]. Since the presence of glycine has been described as pathognomonic for CNC [5,14, 15,19,41]. 1H MRS is considered as helpful, non-invasive method providing additional information which is useful to make CNC recognition, especially in extraventricular location.

The aim of this study was to evaluate the peak at 3.55 ppm in a long echo time recognized as glycine in central neurocytomas and WHO grade II gliomas by means of 1H MRS.

Material and methods

Material

21 consecutive patients with primary brain tumor were included in the analysis. All patients included in the analysis had MR examination at Radiodiagnostics Department at Comprehensive Cancer Centre Maria Sklodowska-Curie Memorial Institute Branch Gliwice between January 2006 and June 2008. WHO grade II glioma group comprised of 19/21 patients (6 females and 13 males, average age 38 ± 9 years). The characterisation of the group is presented in Table 1. Central neurocytoma group comprised of 2/21 patients (female and male, average age 44). The tumor was localized intraventricular in both cases. All of the patients underwent surgery after MR examination and resected tumor was histopathologically diagnosed.

61 healthy volunteers (39 females and 22 males, average age 31 ± 11 years) were consecutively examined at Radiodiagnostics Department at Comprehensive Cancer Centre Maria Sklodowska-Curie Memorial Institute Branch Gliwice or Department of Radiology at Oncology Centre in Bydgoszcz.

All of the MR examinations were performed with the consent of the Local Ethics Committee.

Methods

MR examination of the brain was performed with the 1.5 T scanner. A commercial head coil was used for imaging and spectroscopy. One patient with CNC had a brain examination with use of 3.0 T scanner.

Conventional MR imaging consisted of T1-weighted, T2-weighted images, FLAIR (Fluid-Attenuated Inversion Recovery), PD (Proton Density) and T1-weighted images before and after CE (contrast enhancement).

Proton MR spectroscopy(1H MRS)

1.5 T: 3D CSI PRESS: long TE (TR/TE 1500/135 ms), NSA 1, acquisition time 7.47 min and mean voxel volume 1.3 mL.

3.0 T: 3D CSI PRESS: long TE (TR/TE 2000/144 ms) NSA 1, acquisition time 7.13 min and mean voxel volume 2.7 mL. The T1 relaxation time increase at higher fields, leading to increased signal saturation for a given TR. To maintain the same level of T1 relaxation, we used higher TR for 3.0 T scanner.

In tumors without contrast enhancement, voxels were placed in a central, solid part of area of high signal intesity on T2-weighted images, which corresponds to mass effect. In tumors with contrast enhancement, voxels were placed in a central, solid part of contrast enhancing area.

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787 voxels were included into the analysis in the group of WHO grade II glioma and 74 voxels in the group of central neurocytoma.

We took into account such metabolites as: choline (Cho), creatine (Cr), N-acetylaspartate (NAA) and a single peak at 3.55 ppm in long TE defined as glicyne (Gly). Ratios of Gly/Cr, Gly/Cho and Gly/NAA were calculated for WHO grade II glioma and central neurocytoma group separately. Additionally such metabolites ratios as Cho/Cr, NAA/Cr and Cho/NAA were calculated. Obtained data were analyzed with the LCModel version 6.1-4F. The LCmodel algorithm analyzes the *in vivo* spectrum as a linear combination of individual *in vitro* metabolite spectra that constitute a basis set.

Each metabolite's signal intesity value is assigned to 8 ml voxel size, so it is independent from raw voxel size obtained during in vivo measurements. The estimated standard deviation (%SD) below 20% has been used as a rough criterion for estimates of acceptable reliability. Therefore the presence of the peak at 3.55 ppm was accepted when its SD was less than 20%.

All of the 61 healthy volunteers were examined SVS PRESS, long TE (TR/TE 1500/135 ms, NSA 192, and the average voxel volume 5.0 mL. In 41 out of 61 volunteers an additional 1H MRS was performed with 2D CSI, long TE (TR/TE 1500/135 ms, NSA 4 and the average voxel volume 1.7 mL). Only diagnostic spectra were analysed.

Table I. The clinical characterisation of the group with histologically confirmed WHO II grade gliomas.

Patent	Gender	Age [years]	Histopathological diagnosis	Tumor localization
1	M	52	Astrocytoma diffusum WHO II	cerebral hemisphere
2	M	32	Astrocytoma diffusum WHO II	frontal and parietal lobe
3	M	37	Astrocytoma diffusum WHO II	frontal lobe
4	F	26	Astrocytoma fibrillare WHO II	frontal and temporal lobe
5	M	37	Astrocytoma fibrillare WHO II	cerebral hemisphere
6	M	49	Astrocytoma fibrillare WHO II	temporal lobe
7	M	30	Astrocytoma fibrillare WHO II	frontal lobe
8	M	25	Astrocytoma fibrillare WHO II	medulla oblongata
9	F	38	Astrocytoma fibrillare WHO II	frontal lobe
10	F	43	Glioma mixtum oligoastrocytoma WHO II	frontal lobe
11	F	46	Glioma mixtum oligoastrocytoma WHO II	temporal lobe
12	F	47	Glioma mixtum oligoastrocytoma WHO II	brainstem and cerebellum
13	F	47	Astrocytoma diffusum WHO II	temporal lobe
14	M	39	Astrocytoma fibrillare WHO II	brainstem, subcortical deep structures of the brain
15	M	42	Astrocytoma fibrillare WHO II	parietal lobe
16	M	30	Glioma mixtum oligoastrocytoma WHO II	frontal lobe
17	F	29	Glioma mixtum oligoastrocytoma WHO II	brainstem, subcortical deep structures of the brain, temporal lobe
18	F	42	Oligodendrioglioma WHO II	frontal and temporal lobe
19	M	26	Oligodendrioglioma WHO II	frontal and temporal lobe

Analysis contained:
– 156 voxels obtained from SVS localized in hipocampus 45/156, in cerebellum 74/156, in frontal and temporal lobe 37/156;
– 2456 voxels obtained from 2D CSI localized in thalamus 1048/2456 and in frontal and parietal lobes 1408/2456.

Statistical analysis

Statistical calculations and analyses were performed with Statistical PL software version 7.1 by StatSoft, Inc. Estimation of metabolites ratios between analysed groups was performed with Kolmogorov-Smirnov test for independent experiments. Statistically significant p-levels were assumed as < 0.05.

Results

In 12/19 (63%) WHO grade II gliomas Gly was detected whereas in 7/19 (37%) was not. In these 12 WHO grade II gliomas 646 voxels were analysed, but Gly was observed only in a part of the voxels – 169, which comprise approximately 26% of the tumor volume. Figures 1 and 2 shows the spectrum obtained from 3D CSI in astrocytoma fibrillare with and without distinguished Gly respectively. In none of oligodengrogliomas Gly was observed (Table 2).

In 2 patients with central neurocytoma 74 voxels from tumors were analysed. Gly was distinguished in both tumors in 32 out of 74 voxels which comprise approximately 43% of the tumor volume. Figure 3 shows the spectrum obtained from 3D CSI in central neurocytoma with distinguished Gly.

Mean value of Gly/Cr, Gly/Cho and Gly/NAA ratios were calculated from all voxels in which Gly was distinguished separately for each group (Tables 3A and 3B, Figs. 4-6).

The ratio of Gly/Cr in central neurocytomas was statistically significantly higher than in WHO grade II gliomas (mean$_{CNC}$ 0.62 ± 0.18 vs. mean$_{WHO II}$ 0.37 ± 0.10; $p < 0.001$) but the ratio of Gly/Cho was statistically significantly lower (mean$_{CNC}$ 0.18 ± 0.04 vs. mean$_{WHO II}$ 0.24 ± 0.07; $p < 0.001$). There was no difference between analysed groups in terms of Gly/NAA ratio (mean$_{CNC}$ 0.36 ± 0.09 vs. mean$_{WHO II}$
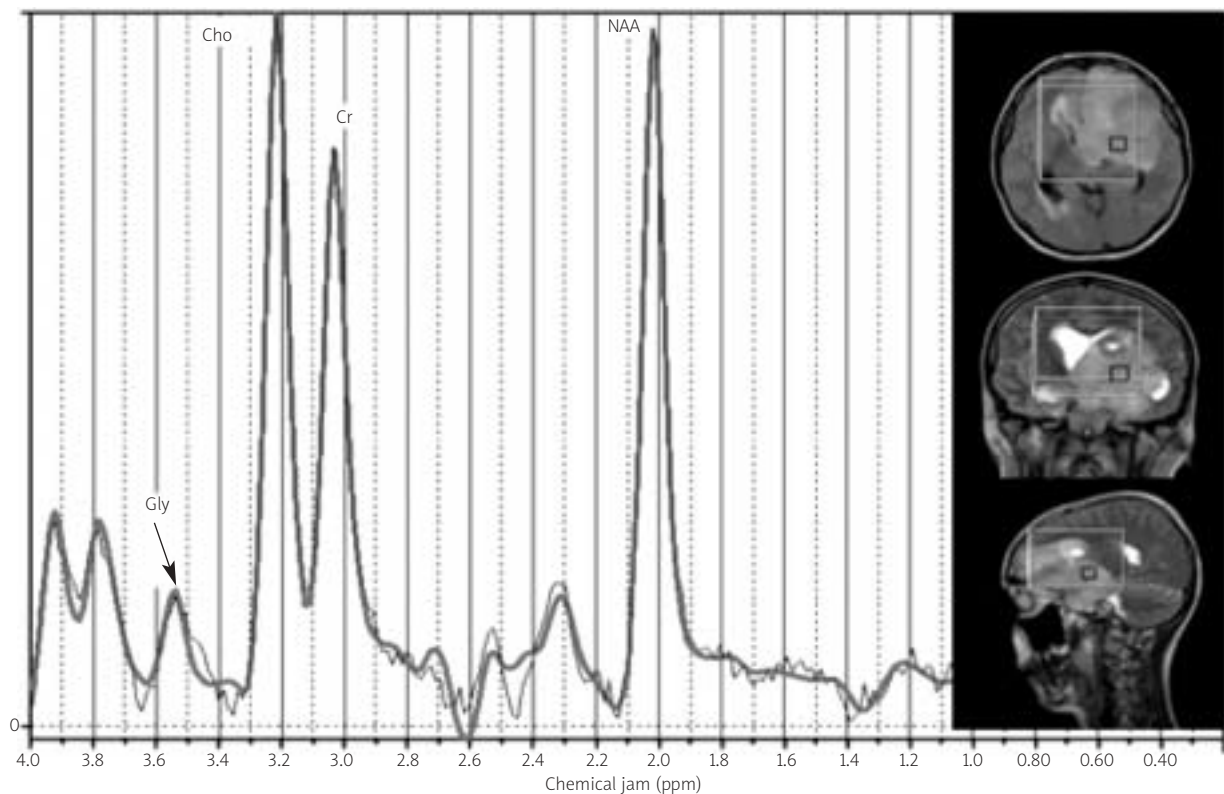

Fig. 1. Astrocytoma fibrillare WHO II. 1H MRS (3D CSI, TE = 135 ms). Gly at 3.55 ppm distinguished.

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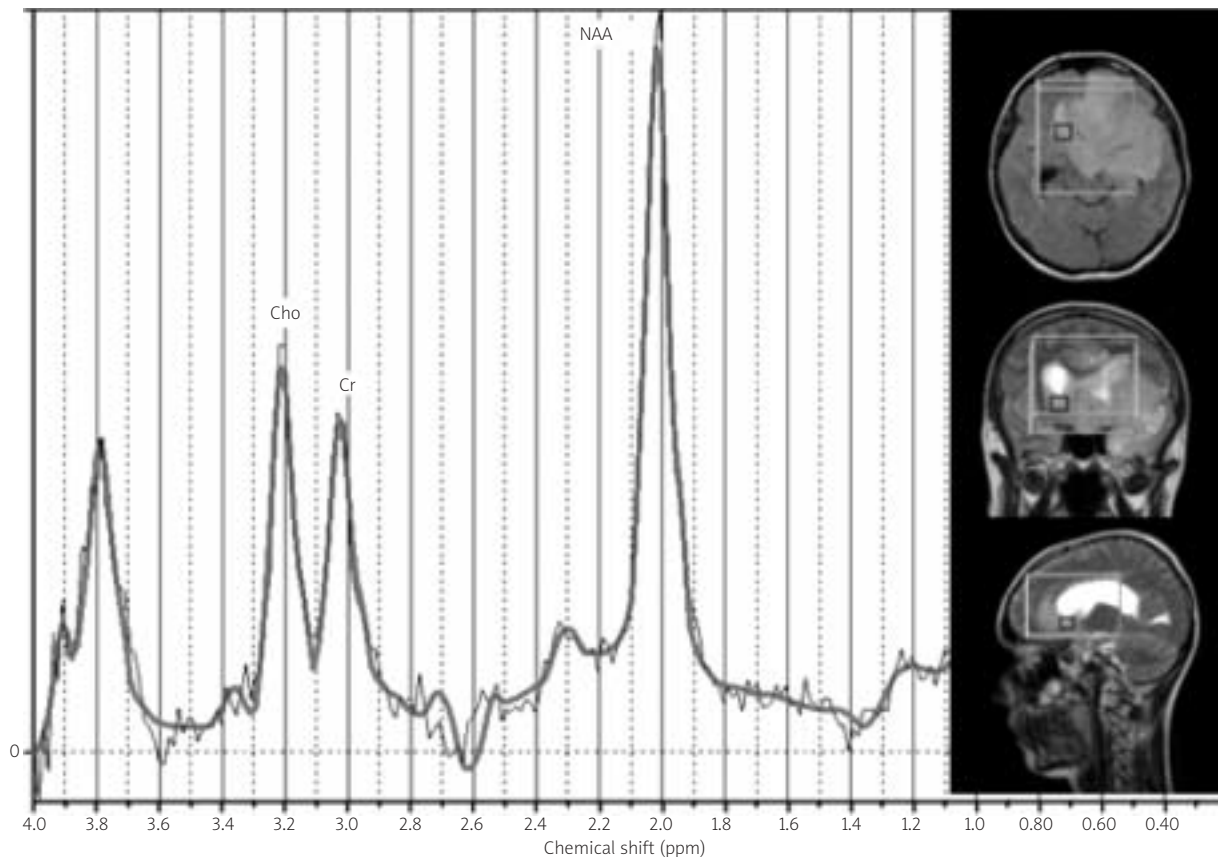

Fig. 2. Astrocytoma fibrillare WHO II. 1H MRS (3D CSI, TE = 135 ms). No Gly at 3.55 ppm distinguished.

0.36 ± 0.14; p = NS). For better understanding of the results additional analysis was conducted and Cho/Cr, NAA/Cr and Cho/NAA ratios were calculated in both analysed groups. It was proved that mean Cho/Cr, NAA/Cr and Cho/NAA ratios were statistically significantly higher in central neurocytomas than in WHO grade II gliomas. Results were presented in Tables 4A and 4B. In the group of 61 volunteers 2612 spectra were analysed. Glycine was found in 7 out of 61 (11.5%) people but only in 8 out of 2612 analysed voxels which comprise 0.3%.

Discussion

Glycine is an amino acid synthesized from serine in the synaptic vesicles which acts as a neuromodulator or antioxidant. It is distributed throughout different parts of central nervous system [11,13,39]. Its concentration in the normal brain range from 0.4 to 1.0 mM [8,30]. Conventional 1H MRS might not be enough to distinguish Gly peak in normal brain. Some authors who distinguished Gly by means of 1H MRS used scan-

ners with magnetic field higher than 3.0 T [7], echo-time-averaged [30] or triple-refocusing filtration [4].

In 1H MRS peak at 3.52-3.57 ppm is assigned to mI and/or Gly [4,8,9,11,14,23]. In short echo time mI resonance as multiplet and overlaps with Gly's methylene-protons (–CH2) groups that co-resonate at 3.55 ppm as a single peak [7,8,11,14,30,37]. It is impossible to separate these metabolites by means of 1.5 T and 3.0 T 1H MRS in short echo time. Gambarot *et al.* proved in 7.0 T 1H MRS with TE 30 ms single peak of Gly resonating between mI multiplet at 3.55 ppm [7]. mI has short and shorter than Gly T2 relaxation time so its contribution to magnetic resonance spectrum is reduced considerably, in longer echo time (TE 100-170 ms). Therefore in long echo time peak at 3.55-3.57 ppm is assigned to Gly rather than to mI [4,7,8,11,14,30,37].

Gly is considered as characteristic feature for CNC, but it might be detected in a low and high grade gliomas [5,11,14-17,19,20,36,41]. Higher level of Gly was detected in high grade gliomas than in low ones, which was claimed by Hattingten *et al.* [11], by Lehn-

hardt'a *et al.* as well as Tugnoli *et al.* during *in vitro* studies [20,36]. In our material Gly in long TE was observed in 12 out of 19 (63%) WHO grade II gliomas. Gly was present in astrocytomas – 9/12 (75%) as well as in oligoastrocytomas – 3/12 (25%). We didn't find Gly in none of 2 oligodendrogliomas. It might be cau-

Table II. WHO grade II glioma group in terms of Gly detection.

Patient	Histopathological diagnosis	Peak of the Gly "+" if detected "–" if not detected
1	Astrocytoma diffusum WHO II	+
2	Astrocytoma diffusum WHO II	+
3	Astrocytoma diffusum WHO II	+
4	Astrocytoma fibrillare WHO II	+
5	Astrocytoma fibrillare WHO II	+
6	Astrocytoma fibrillare WHO II	+
7	Astrocytoma fibrillare WHO II	+
8	Astrocytoma fibrillare WHO II	+
9	Astrocytoma fibrillare WHO II	+
10	Glioma mixtum oligoastrocytoma WHO II	+
11	Glioma mixtum oligoastrocytoma WHO II	+
12	Glioma mixtum oligoastrocytoma WHO II	+
13	Astrocytoma diffusum WHO II	–
14	Astrocytoma fibrillare WHO II	–
15	Astrocytoma fibrillare WHO II	–
16	Glioma mixtum oligoastrocytoma WHO II	–
17	Glioma mixtum oligoastrocytoma WHO II	–
18	Oligodendroglioma WHO II	–
19	Oligodendroglioma WHO II	–

sed by small number of these specimen in our material. Other authors also didn't find Gly in oligodendrogliomas [36,17].

Of note is the fact that the peak of Gly was detected only in a part of the tumor volume (approximately in 26% of the ananlysed voxels in WHO grade II gliomas). To our konowledge a report about heterogeneity of WHO II gliomas considering glycine presence/absence has not been yet published.

Central neurocytoma is a rare tumor of central nervous system mostly occurring in young adults [5,21,24]. Approximately 70% of CNC is diagnosed in patients between the ages of 20 and 40 years [28]. It makes up 0.25-0.5% of intraaxial brain tumors [39,41] and corresponds to WHO grade II [24]. It was described for the first time in 1982 by Hassoun [10]. CNC is typically located in the lateral ventricles and/or the third ventricle, in the foramen of Monro and its characteristic feature is the attachment to the septum pellucidum [5,22,24,27,28,39,42]. Extraventricular location is rather rare [24,40]. Possibility of differentiation would be particularly precious for rare – extraventricular localisation of infiltration [1,29,32,33]. As previously mentioned, the Gly peak at 3.55 ppm might be detected in different primary brain tumors, but it is more characteristic feature for CNC [5,14-16,19,41]. On the other hand lack of distinct glycine in 1H MRS doesn't exclude central neurocytoma type [15,18]. Using SVS 1H MRS Kocaoglu *et al.* found Gly in only 1 out of 7(14.3%) CNC and Kanamori *et al.* in 1 out of 3 (33%) CNC [15,18]. The reason for the

Table IIIB. Differences of analysed metabolites ratios among analysed groups – part one.

Metabolites ratio	Dependence between groups	p value
Gly/Cr	WHO II < CNC	< 0.001
Gly/Cho	WHO II > CNC	< 0.001
Gly/NAA	WHO II ≃ CNC	NS

Table IIIA. Mean values of the metabolites ratios in WHO grade II glioma group and central neurocytoma group – part one.

Group	1H MRS		
	Gly/Cr	Gly/Cho	Gly/NAA
WHO II grade glioma (Mean ± SD)	0.37 ± 0.10	0.24 ± 0.07	0.36 ± 0.14
Central neurocytoma (Mean ± SD)	0.62 ± 0.18	0.18 ± 0.04	0.36 ± 0.09

Table IVA. Mean values of the metabolites ratios in WHO grade II glioma group and central neurocytoma group – part two.

Group	1H MRS		
	Cho/Cr	NAA/Cr	Cho/NAA
WHO II grade glioma (Mean ± SD)	1.60 ± 0.45	1.08 ± 0.35	1.58 ± 0.80
Central neurocytoma (Mean ± SD)	3.84 ± 1.19	1.69 ± 0.43	2.17 ± 0.62

Table IVB. Differences of analysed metabolites ratios among analysed groups – part two.

Metabolites ratio	Dependence between groups	p value
Cho/Cr	WHO II < CNC	< 0.001
NAA/Cr	WHO II < CNC	< 0.001
Cho/NAA	WHO II < CNC	< 0.001

absence of Gly peak at 3.55 ppm in 1H MRS examination at patients with CNC, can be the fact that glycine can exist only in a part of tumor volume. Our material consist two patients with CNC in intraventricular localisation. Gly peak appeared in both tumors but only in part of the tumor volume (approximately in 43% of the ananlysed voxels). Because of this SVS
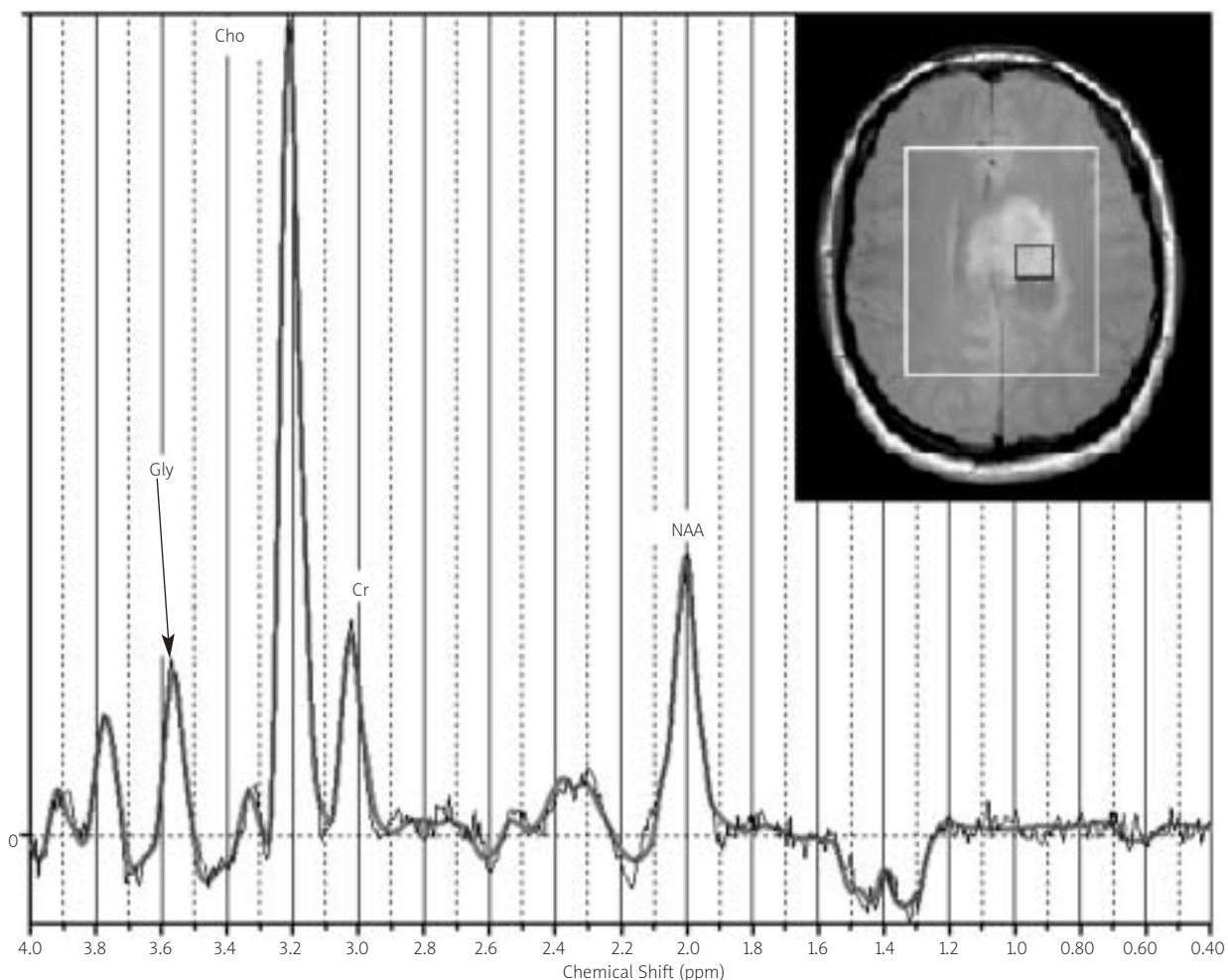

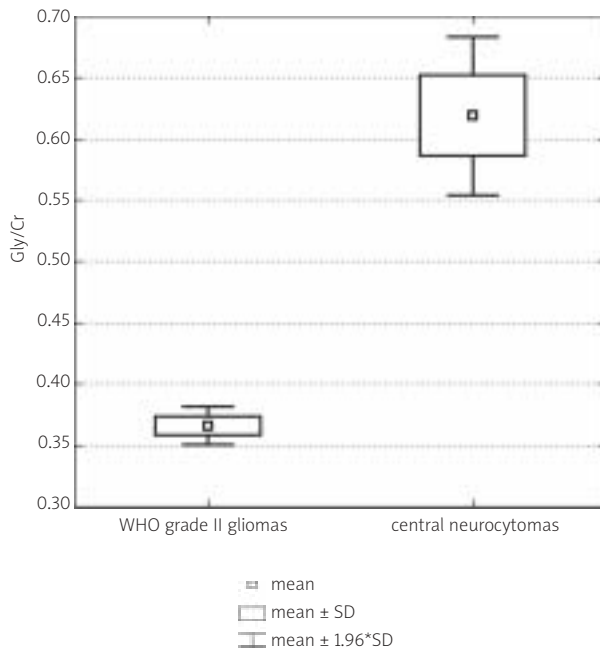**Fig. 3.** Central neurocytoma 1H MRS; A – 3D CSI, TE 144 ms. Gly peak at 3.55 ppm distinguished.

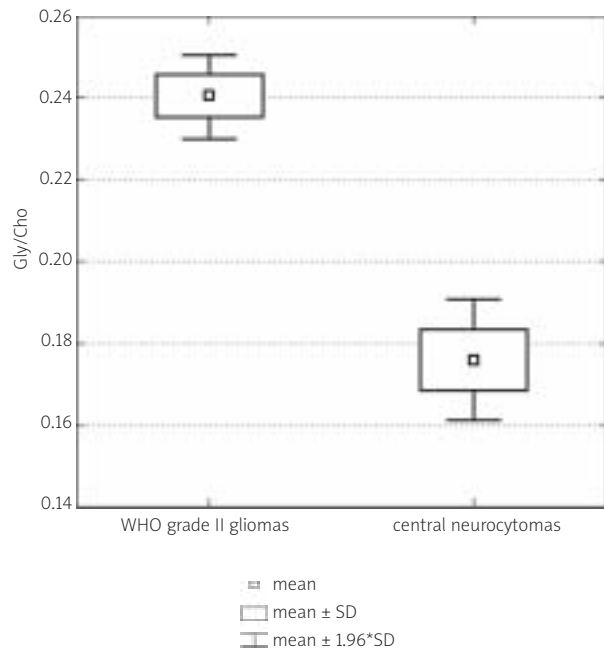**Fig. 4.** Mean Gly/Cr ratio in WHO grade II glioma and central neurocytoma group.

Fig. 5. Mean Gly/Cho ratio in WHO grade II glioma and central neurocytoma group.

might not be enough to prove presence or absence of Gly. Krishnamoorthy *et al.* distinguished peak at 3.55 ppm in long echo time (TE 135 ms) in all three analysed central neurocytomas. For these tumors MR spectroscopy was performed with a multivoxel method but there isn't any information whether Gly was observed in all voxels [19].

The analysis of the Gly/Cr, Gly/Cho, Gly/NAA ratio in central neurocytomas as well as in WHO grade II gliomas was also proposed by other authors but comparison between those two groups was not conducted [16,20,39]. Kim *et al.* reported higher Gly/Cr, Gly/Cho and Gly/NAA ratios, Ueda *et al.* higher Gly/Cr ratio in CNC than our results. It might be caused by different 1H MRS methods: Kim *et al.*, Ueda *et al.* used single voxel spectroscopy whereas we used multivoxel one. Lehnhardt *et al.* presented lower Gly/Cr ratio in low grade gliomas than we obtained. But Lehnhardt *et al.* carried in vitro study and we *in vivo* one. We obtained higher mean Gly/Cr ratio in the central neurocytoma group than in the WHO grade II glioma one. Furthermore Gly/Cho ratio was lower in the central neurocytomas than in the WHO grade II gliomas. It might be explained by higher Gly and Cho
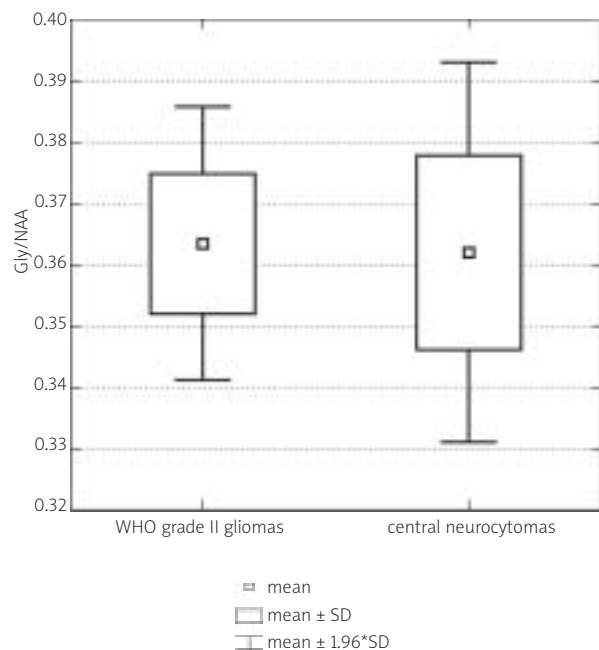

Fig. 6. Mean Gly/NAA ratio in ratio in WHO grade II glioma and central neurocytoma group.

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peak in the central neurocytomas in comparsion with WHO grade II gliomas. In the additionally performed analysis we obtained higher Cho/Cr ratio in central neurocytomas group than WHO grade II one. We also observed equal Gly/NAA ratio in both compared groups. These results might be due to higher NAA peak in central neurocytomas group than WHO grade one as it was proved by higher NAA/Cr and Cho/NAA ratios in the central neurocytoma group.

In our analysis we estimated the presence of Gly at 3.55 ppm in 1H MRS in long echo time only in only in 8 out of 2616 voxels which comprise 0.3% and it seems rather coincidental result, which should be avoided.

Conclusions

Glycine is found in WHO II grade gliomas as well as in central neurocytomas, but only in a part of a tumor volume. It is necessary to perform 1H MRS of the whole tumor volume to confirm/exclude the presence of glycine. Glycine in a normal brain can not be identified by means of conventional 1H MRS performed by means of 1.5 T or 3.0 T scanners.

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