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## Single-voxel proton spectroscopy of cortical tubers in children with tuberous sclerosis complex

Widma spektroskopii wodorowej guzów korowych w przebiegu stwardnienia guzowatego u dzieci

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### Summary

**Background:**

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem disorder with two gene loci located on chromosomes 9q34 (TSC1) and 16p13 (TSC2). Brain abnormalities in TSC include cortical tubers, subependymal nodules, giant cell astrocytomas, and white matter lesions. Cortical tubers present disordered focal neocortical formation. However, their biology remains to be elucidated. Recently, proton magnetic resonance spectroscopy has been clinically applied to the differential diagnosis of brain changes as a noninvasive neuroimaging tool. The purpose of this study was to investigate cortical tubers by single-voxel proton spectroscopy.

**Material/Methods:**

Twenty-four children with TSC were examined using a 1.5T scanner with a standard head coil. The group of patients consisted of 12 girls and 12 boys aged 3 weeks to 28 years (median: 8.66 years). Ten healthy children (examined for other reasons, with normal MR images) were the control group. Integrated MR/MRS examinations were performed. Proton MR spectroscopy images were obtained using single-voxel point resolved spectroscopy, the PRESS technique with TE=35 ms and TR=1500 ms.

**Results:**

Proton MR spectroscopy of cortical tubers revealed increased mI/Cr ratio (1.023 versus 0.553 in healthy children) and slightly decreased NAA/Cr (0.952 vs. 1.268) and NAA/Cho ratios (0.948 vs. 1.208) in all the spectra of TSC patients. The Cho/Cr ratio was almost the same as in the control group (1.079 vs. 1.058). Lactate peaks were present in ten cortical tubers.

**Conclusions:**

Proton spectroscopy can be useful in the examination of cortical tubers in TSC as a noninvasive method to investigate neurochemistry of the brain.

**Key words:**

tuberous sclerosis complex • single-voxel proton spectroscopy • cortical tubers • children • magnetic resonance imaging

**PDF file:**

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## Background

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem disorder with two gene loci located on chromosomes 9q34 (TSC1) and 16p13.3 (TSC2). Brain abnormalities in TSC include cortical tubers (cerebral hamartomas), subependymal nodules, giant cell astrocytomas and white matter lesions. Cortical tubers present disordered focal neocortical formation. Histologically, they consist of bizarre giant cells, dense fibrillary gliosis and diminished myelin sheaths. Baloon cells may be seen sometimes like in the focal cortical dysplasia [1]. However, their biology remains to be elucidated.

On MR imaging the signal intensity of the tubers depend on age of patients and sequences used. Malignant degeneration of cortical tubers is extremely rare.

Recently, proton magnetic resonance spectroscopy has been clinically applied to the differential diagnosis of brain changes as a noninvasive neuroimaging tool. The main metabolites evaluated are N-acetyl aspartate (NAA), choline (Cho), creatine (Cr), myoinositol (mI), lactate (lac). NAA group (mainly N-acetyl aspartate) is considered a marker of neurons. Level of creatine remains relatively unchanged and it is used as internal standard to compare other metabolites. Cho is a major component of cell membranes and it is often related to tumor development. Myoinositol is abundant in glial cells and is therefore considered to be glial cell marker. Peak of lactate can occur in settings with anaerobic metabolism and ischemia and it is not seen in the healthy brain tissue.

The purpose of this study was to investigate cortical tubers by single-voxel proton spectroscopy.

## Material and methods

We examined 24 children who met clinical diagnostic criteria for tuberous sclerosis complex. The group of patients consisted of 12 girls and 12 boys, aged 3 weeks to 28 years (mediana 8.66 years). The control group consisted of ten healthy children with normal MR images, aged 3 to 16 years (mediana 8.5 years), examined for other reasons.

Integrated MR/MRS examinations were performed. MR examinations were performed with a 1.5 T scanner with standard head coil. The basic imaging protocol included

axial images: SET1WI (500-670/16/1-2 [TR-repetition time/TE-echo time/excitations]), FSEPD,T2WI (15/80/3500-3800/1), FSE FLAIR (1800/13700/112/1-2) [IR-inversion time/TR/TE/excitations] and coronal FLAIR images. Matrix size was 256x256 and 256x192, field of view: 22-23mm, section thickness 4-5mm, intersection gap 1mm.

T1-weighted axial contrast-enhanced images were obtained in each patient (Gd-DTPA was administered intravenously in a standard dose 0.1mmol/cc).

Proton MR spectroscopy images were obtained using single-voxel point resolved spectroscopy - PRESS technique. The technical details were as follows: TE=35ms, TR=1500ms, NSA=192, voxel size: 20 x 20 x 20 mm, scan time: 5 min 24 s.

We performed spectroscopy from two different tubers in 4 children, a total number of spectra was 28.

Spectroscopic data were analyzed with the manufacturer's spectroscopy software package. Voxels were placed in cortical tubers, which were indicated on FLAIR images. The main metabolites: NAA, Cr, Cho, mI and their ratios (NAA/Cho, Cho/Cr, mI/Cr, NAA/Cho) were evaluated and compared to control children. To avoid artifacts the largest supratentorial cortical tubers (seen on FLAIR images) were selected to HMRS examinations.

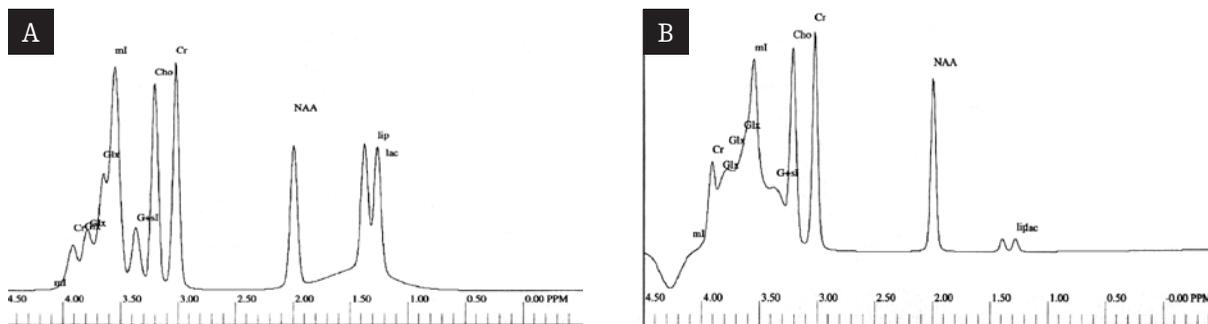
## Results

Our group of patients consisted of 12 girls and 12 boys; clinical findings are summarized in table 1.

Proton MR spectroscopy of cortical tubers revealed increased mI/Cr ratio (1.023 versus 0.553 in healthy children) and slightly decreased NAA/Cr (0.952 vs. 1.268) and NAA/Cho ratios (0.948 vs. 1.208) in all the spectra of TSC patients. Cho/Cr ratio was almost the same as compared to the control group (1.079 vs 1.058). Lactates peaks were present in ten cortical tubers.

Proton spectra from cortical tubers of patients with TSC are shown in Fig. 1a, b.

The analysis of cortical tubers' spectra in our patients demonstrated metabolic differences between these lesions and corresponding anatomic structures in healthy children (tab. 2).



**Figure 1.** HMR spectra from the cortical tubers. **A.** Decrease in NAA, increase in mI peak. Lactates are present. **B.** Decrease in NAA, increase in mI peaks. **Rycina 1.** Widma spektroskopii wodorowej guzów korowych. **A.** obniżenie piku NAA, podwyższenie piku mI, obecne mleczany. **B.** obniżenie piku NAA, podwyższenie piku mI.

**Table 1.** Clinical findings.  
**Tabela 1.** Objawy kliniczne.

Pts	age	sex	mental ability	epilepsy type
1.	0.5	M	normal	none
2.	3.25	M	mild	infantile spasms
3.	16	F	moderate	infantile spasms, partial seizures
4.	8.33	M	moderate	infantile spasms
5.	10	F	severe	partial seizures
6.	28	F	mild	infantile spasms, partial seizures
7.	0.83	M	normal	infantile spasms
8.	0.08	F	normal	infantile spasms
9.	11	M	severe	infantile spasms, partial seizures
10.	17.33	F	normal	partial seizures
11.	5.75	M	normal	complex partial seizures
12.	1.5	F	mild	infantile spasms
13.	14.17	F	mil	partial seizures
14.	20.58	F	mild	infantile spasms, tonic-clonic seizures
15.	19.67	M	mild	partial seizures
16.	17.08	M	moderate	complex partial seizures
17.	6.08	M	mild	tonic-clonic seizures
18.	13.08	F	normal	infantile spasms
19.	1.83	M	mild	myoclonic seizures, tonic-clonic seizures
20.	16.58	M	mild	partial seizures
21.	3.5	F	moderate	infantile spasms, s.Lennox-Gastaut
22.	9	F	mild	infantile spasms, partial seizures
23.	7.58	M	mild	infantile spasms
24.	3.41	F	mild	infantile spasms, tonic-clonic seizures

## Discussion

Proton magnetic resonance spectroscopy is a noninvasive method for *in vivo* imaging of brain metabolism.

We placed MRS voxels precisely in cortical tubers so our results reflected changes inside tubers.

Decrease in the NAA peak represents decreased neuronal viability and function as well as neuronal loss. Lower peak of NAA and decreased NAA/Cr ratios in TSC patients may be caused by gliosis and immature neurons inside cortical tubers. Changes in NAA peaks and decrease in the ratio of NAA to Cr suggest a diminished neurons number in cortical tubers.

The lower NAA/Cho and NAA/Cr ratios were found in cortical tubers in patients investigated by authors in previously

published papers [2,3,4]. Marked decrease in NAA was found in biopsy samples from three adult patients with TSC investigated *in vitro* by Aasly et al. [4].

Increased mI levels and mI/Cr ratios indicate glial proliferation, gliosis and demyelination. Increased mI/Cr ratio was also found in a papers published by Mizuno and Tarasow [3,5].

No significant differences were noted in Cho/Cr ratios in cortical tubers and healthy brain tissue. The same results were obtained by Mukonoweshunero, he mentioned that none of the tubers showed pattern typical of a neoplasm [2]. The peak of choline is markedly increased in tumors as it reflects membrane turnover. Therefore the Cho/Cr ratios were used to differentiate cortical tubers from neoplastic lesions in some cases.

**Table 2.** Single-voxel proton spectroscopic findings (metabolite ratios).**Tabela 2.** Stosunki metabolitów otrzymanych widm spektroskopii wodorowej pojedynczego woksela

	TSC patients			Healthy children		
	from	to	mediana	from	to	mediana
NAA/Cr	0.5369	1.2964	0.9135	1.0091	1.3274	1.2676
NAA/Cho	0.3479	1.4528	0.9286	1.0402	1.2881	1.2078
ml/Cr	0.5888	1.4243	1.0803	0.4321	0.7711	0.5532
Cho/Cr	0.7941	1.5432	1.0256	0.8683	1.4021	1.0582

Lactate were present in ten of TSC patients.

Sener investigated a 3-month-old child with an increased Cho/Cr ratio suggesting a neoplasm; HMRS performed 7 months later revealed decreased NAA/Cr ratio and slightly increased Cho/Cr as compared to the surrounding brain tissue which excluded a neoplastic condition [6].

Presence of lactate may reflect degeneration and chronic ischemia within the tubers. Lactic acid is the end product of glycolysis and lactate peak can occur in anaerobic metabolism (in mitochondrial disease, tumors, acute ischemia, infarction) [2,7]. Yapici showed lactate peak in the epileptic foci and in the tubers without epileptic activity (investigated by EEG). It was found more frequently in the first case (46.7%) than in the latter (26.7%).

In the paper presented by Mukonoweshuro no lactate was identified in any cortical tuber but the author mentioned that some cortical tubers may express lactate because of central degeneration [2].

### Conclusion

Proton spectroscopy provides a noninvasive method to investigate the neurochemistry of the brain.

HMRS shows differences between cortical tubers in cases of TSC and corresponding areas in healthy children.

This is a helpful method to differentiate atypical cortical tubers from neoplastic lesions and to improve diagnosis in TSC patients.

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