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Differential diagnosis of intracranial meningiomas based on magnetic resonance spectroscopy

Diagnostyka różnicowa oponiaków wewnątrzczaszkowych w spektroskopii rezonansu magnetycznego

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Abstract

Background and purpose: To determine *in vivo* magnetic resonance spectroscopy (MRS) characteristics of intracranial meningiomas and to assess MRS reliability in meningioma grading and discrimination from tumours of similar radiological appearance, such as lymphomas, schwannomas and haemangiopericytomas.

Material and methods: Analysis of spectra of 14 patients with meningiomas, 6 with schwannomas, 2 with lymphomas, 2 with haemangiopericytomas and 17 control spectra taken from healthy hemispheres.

Results: All the patients with meningiomas had a high Cho signal (long TE). There were very low signals of Naa and Cr in the spectra of 10 patients. A reversed Ala doublet was seen only in 2 cases. Four patients had a negative Lac signal, whereas 3 had high Lac-Lip spectra. Twelve spectra showed high Cho signals (short TE). In one case the Cho signal was extremely low. All spectra displayed a very low Cr signal, but high Glx and Lac-Lip signals. Ala presence was found only in 3 patients. The mean Cho/Cr ratio (PRESS) was 5.97 (1.12 in normal brain, $p < 0.05$). Lac-Lip was present in all the meningiomas (STEAM). The Ala signal was seen only in 2 spectra with long TE and in 3 sequences of the short TE

Streszczenie

Wstęp i cel pracy: Charakterystyka spektroskopii rezonansu magnetycznego (*magnetic resonance spectroscopy* – MRS) u chorych na oponiaki wewnątrzczaszkowe i ocena przydatności tego badania w przedoperacyjnej diagnostyce stopnia złośliwości oponiaków oraz różnicowaniu oponiaków z nowotworami o podobnych cechach radiologicznych, takimi jak chłoniaki, nerwiaki osłonkowe i obłoniaki.

Materiał i metody: Analiza widm MRS u 14 chorych z oponiakami, 6 z nerwiakami, 2 z chłoniakami i 2 z obłoniakami oraz 17 widm kontrolnych uzyskanych ze zdrowych półkul mózgu.

Wyniki: Wszyscy chorzy z oponiakami mieli wysoki sygnał Cho (przy długim TE). U 10 chorych występował bardzo niski sygnał Naa i Cr. U 2 pacjentów stwierdzono odwrócony dublet Ala. Cztery osoby miały ujemny sygnał Lac, a 3 wysokie widma Lac-Lip. Wysoki sygnał Cho zaobserwowano u 12 chorych (przy krótkim TE), u jednego pacjenta sygnał ten był krańcowo niski. Wszystkie widma wykazywały bardzo niski sygnał Cr przy wysokich sygnałach Glx i Lac-Lip. Obecność Ala odnotowano tylko u 3 chorych. Średni wskaźnik Cho/Cr (PRESS) wyniósł 5,97 (1,12 w niezmienionym mózgu; $p < 0,05$). Lac-Lip był obecny we wszystkich oponiakach (STEAM). Sygnał

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sequences. There were both β/γ-Glx and α-Glx/glutathione signals in all 14 meningiomas.

Conclusions: MRS is unable to discriminate low and high grade meningiomas. The method seems to be helpful in discriminating lymphomas (absent Glx signal), schwannomas (mI signal in the short TE sequences) and haemangiopericytomas (presence of mI band) from meningiomas.

Key words: MRS, meningioma, schwannoma, lymphoma, haemangiopericytoma.

Ala zaobserwowano jedynie w 2 widmach przy długim TE i w 3 sekwencjach przy krótkim TE. Sygnały α-Glx/glutation oraz β/γ-Glx były obecne u wszystkich chorych z oponiakami.

Wnioski: Badanie MRS nie pozwala na określenie stopnia złośliwości oponiaka. Metoda wydaje się przydatna w diagnostyce różnicowej oponiaków i innych podobnych radiologicznie nowotworów: chłoniaków (brak sygnału Glx), nerwiaków osłonkowych (sygnał mI przy krótkim TE) oraz obłoniaków (obecność pasma mI).

Słowa kluczowe: MRS, oponiak, nerwiak osłonkowy, chłoniak, obłoniak.

Introduction

Meningiomas are common intracranial tumours accounting for 14% to 19% of all primary intracranial neoplasms [1]. The principal diagnostic method of choice is magnetic resonance imaging (MRI), whereas *in vivo* magnetic resonance spectroscopy (MRS) is an auxiliary measure which helps to confirm the diagnosis and allows identification of other radiologically similar neoplasms. There are several reports on the association between MRS spectra and histopathology of brain tumours [2-5]. Furthermore, it has been suggested that combining MRS with MRI improves the accuracy of the diagnosis as compared to MRI alone [6].

The aim of this study was to determine *in vivo* MRS characteristics of meningiomas in patients operated on at the Department of Neurosurgery, Medical University of Lodz, Poland and to compare these data with reports available in the literature, as well as to assess MRS reliability in meningioma grading and discrimination from tumours of similar radiological appearance, such as lymphomas, schwannomas and haemangiopericytomas.

Material and methods

The study involved 89 patients operated on for cerebral neoplasms at the Department of Neurosurgery of the Medical University of Lodz. There were 38 males and 51 females; age ranged from 19 to 75 years. The study evaluated only patients with medium and large tumours, i.e., cases in which the investigator was able to set a voxel volume from 1 to 8 cubic centimetres. All patients gave informed consent to be involved in this study. The examination protocol has been accepted by the University Bioethical Committee for Experiments on Human Subjects. The MR examinations were carried out as part of the eTumour project (LSHC-CT-2004-503094) – Web Accessible MR Decision Support System For Brain Tumour Diagnosis And Prognosis, Incorporating *In Vivo* And Ex Vivo Genomic And Metabolimic Data (http://cordis.europa.eu/fetch?).

The patients had an MRS examination a day prior to the tumour surgery performed by the Siemens Magnetom Vision scanner with a magnetic flux density of 1.5 T. Firstly, T1-weighted images of a tumour were obtained in three planes (coronal, sagittal and axial) after intravenous administration of the contrast medium, i.e. gadolinium. Subsequently, the voxel was set in a solid and most strongly contrast-enhancing part of a tumour (Fig. 1A-C). The MRS examination was done by means of single voxel spectroscopy (SVS), employing both a short echo time (STEAM sequence with TE = 30 ms or PRESS sequence with TE = 30 ms) and a long echo time (PRESS, TE = 136 ms or PRESS, TE = 135 ms). In both instances, the repetition time (TR) was 2000 ms. On average, 256 signal acquisitions were done in each sequence.

The control spectra of normal brain were obtained from the voxel placed in healthy cerebral hemispheres of 17 patients. All spectra were processed by the computer program Magnetic Resonance User Interface (MRUI, v.3) according to the protocol of the eTumour project [7]. The processing included synchronization of the spectrum phase with the reference spectrum representing only the signal of water, apodisation and removing the signal of water employing the method of Hankel Lanczos singular values decomposition (HLSVD).

Qualitative analysis of the spectra included recognition of signals from the following metabolites: *N*-acetyl aspartate (Naa, chemical shift equals 2.02 ppm), choline (Cho – 3.22 ppm), creatinine (Cr – 3.02 ppm), alanine (Ala – 1.48 ppm), myo-inositol (mI – 3.56 ppm), glutamate (Glx – 2.35 ppm), lipids (Lip – 0.9 ppm and

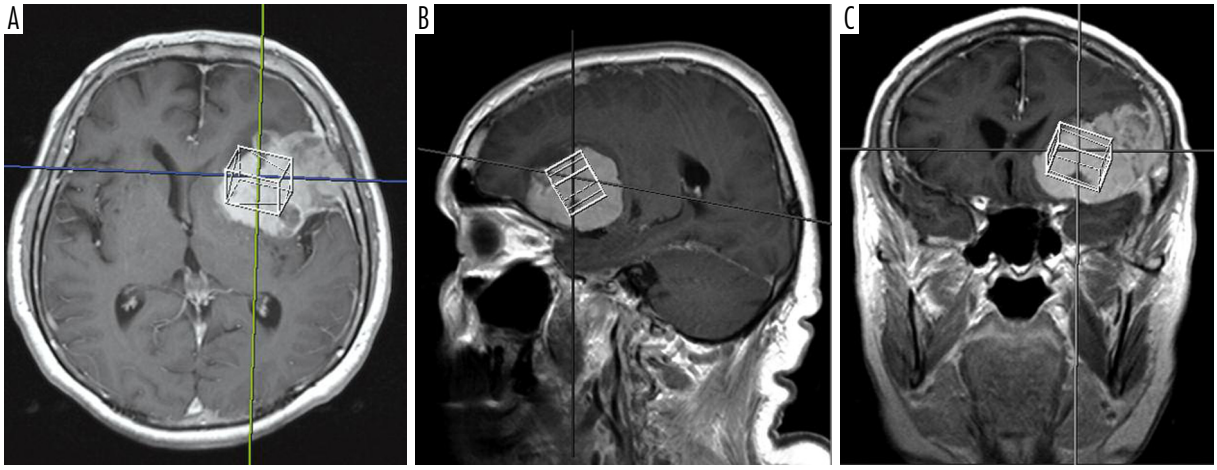

Fig. 1. The voxel placed in the solid and enhancing part of meningioma shown in three planes: (A) transverse, (B) sagittal, (C) coronal

1.3 ppm), and lactates (Lac – 1.33 ppm). The Advanced Method for Accurate, Robust and Efficient Spectral Fitting (AMARES) [8] was used for quantitative analysis. Its results were given as relative values, i.e., fractions of the signal amplitudes: Cho/Cr, Naa/Cr, Cho/Naa, mI/Cr. Contents of lactates and lipids were looked at together, as a Lac-Lip mixture [9,10], and determined by means of semi-quantitative method: absent (–), present (+), or high (+++) [11]. Neuropathological diagnosis was given in accordance with the WHO classification of brain tumours [12]. The results were compared with those obtained from the normal brain and among the examined tumours.

In the examined group, there were 26 patients with glioblastomas, 17 with cerebral metastases, 14 with meningiomas, 3 with oligodendrogliomas, 3 with anaplastic oligodendrogliomas, 6 with fibrillary astrocytomas, 4 with anaplastic astrocytomas, 2 with pilocytic astrocytomas, 2 with haemangiopericytomas, 2 lymphomas, 6 schwannomas and single patients with Lhermitte-Duclos disease, choroid plexus papilloma, pituitary adenoma and, finally, chondroma.

In view of the small numbers of patients, Mann-Whitney *U*-test was used for statistical analysis. The differences were considered statistically significant for $p \leq 0.05$.

Results

Meningiomas were found in 14 patients: 2 males and 12 females who were 22 to 70 years old (mean age, 53 years). The most frequent histopathological diagnosis was fibrous meningioma (WHO grade I) in 4 patients and atypical meningioma (WHO grade II) also in 4 cases. Two patients had meningothelial meningioma (WHO grade I). There were single cases of rhabdoid meningioma (WHO grade III), psammomatous, secretory and transitional meningiomas (all WHO grade I). The clinical details are given in Table 1.

Table 1. Clinical data of patients with meningiomas

No.	Age	Sex	Histopathology	Tumour location
1.	22	F	Atypical	Parasagittal
2.	53	F	Meningothelial	Convexity
3.	61	F	Atypical	Sphenoid ridge
4.	51	F	Secretory	Parasagittal
5.	70	F	Meningothelial	Anterior fossa
6.	51	F	Fibrous	Cerebellopontine angle
7.	61	F	Transitional	Parasagittal
8.	59	F	Fibrous	Parasagittal
9.	55	F	Fibrous	Convexity
10.	61	F	Psammomatous	Cerebellopontine angle
11.	24	M	Atypical	Convexity
12.	53	F	Atypical	Posterior fossa
13.	59	F	Fibrous	Parasagittal
14.	58	M	Rhabdoid	Sphenoid ridge

F – female; M – male

In the long TE sequences, all the patients had a high Cho signal. In the spectra of 10 patients, there were very low signals of the cerebral metabolites, i.e., Naa and Cr. A reversed Ala doublet was seen only in 2 cases. In 4 patients we noted a negative Lac signal, whereas in 3 subjects, high Lac-Lip spectra were observed.

Table 2. Clinical data of patients with neoplasms of radiological appearance similar to meningiomas

No.	Age	Sex	Histopathology	Tumour location
1.	44	M	Haemangiopericytoma	Parasagittal
2.	48	M	Haemangiopericytoma	Anterior fossa
3.	56	F	Lymphoma	Frontal lobe
4.	45	F	Lymphoma	Parietal lobe
5.	55	F	Schwannoma	Cerebellopontine angle
6.	50	M	Schwannoma	Cerebellopontine angle
7.	27	F	Schwannoma	Cerebellopontine angle
8.	45	F	Schwannoma	Cerebellopontine angle
9.	64	F	Schwannoma	Cerebellopontine angle
10.	45	F	Schwannoma	Cerebellopontine angle

F – female; M – male

In the short TE sequence, 12 spectra showed high Cho signals. In one case, the Cho signal was extremely low. All spectra displayed a very low Cr signal, high Glx signals in both ranges (2.05-2.5 ppm and 3.65-3.8 ppm) and a Lac-Lip signal (high in 3 cases). Ala presence was found only in 3 patients.

Due to the very low Cr and Naa signals, the Cho/Cr ratio could be calculated only in 3 patients from the spectra obtained in the long TE sequence. Its mean value was 5.97 ± 0.83. The Cho/Naa ratio was obtained only in one case, the long TE sequence giving the result of 2.1.

The clinical characteristics of patients with tumours that may mimic meningiomas in MRI (i.e. lymphomas, haemangiopericytomas and schwannomas) are given in Table 2.

Discussion

The typical spectrum for meningioma is characterized by a high Cho signal with very low Cr and Naa signals and presence of Ala [13] (Fig. 2). Moreover, in the short TE sequences, there is a Glx band in the range of 2.1-2.5 ppm as well as a Lac-Lip signal [13] (Fig. 3). These features allow discrimination of meningiomas from other neoplasms in up to 94% of cases [13,14]. Similarly to other neoplasms, the increase in Cho contents results from a larger amount of cellular membranes which, in turn, depends upon cellular density of the tumour. In the examined tumours, the mean Cho/Cr ratio calculated in the PRESS sequence was 5.97 (in normal brain this ratio was 1.12, $p < 0.05$).

A low concentration of neuronal metabolites (Cr and Naa) in meningiomas is expected, taking into account the fact that these tumours do not contain neurons. The only exceptions may be seen in meningiomas invading the nervous tissue. In our material, Cr and Naa signals were present only in 3 out of 14 cases.

Lac-Lip was present in all the meningiomas in the STEAM sequence, which is consistent with published data [13]. A high signal was observed only in 3 cases (fibrous, atypical and secretory meningiomas). According to the literature, in quantitative analysis there is no statistically significant difference in Lac-Lip contents in meningiomas in comparison with other cerebral tumours [15]. However, Japanese authors proved that a high Lac-Lip signal is characteristic for anaplastic and atypical meningiomas [16]. In the same article, the authors stated that if the high Lac-Lip signal is present in a meningioma of WHO grade I, then such a tumour has a high proliferation index (MIB-1 labelling index).

Alanine is a metabolite seen only in meningiomas [17], but does not occur in all spectra [18,19]. In our patients, the Ala signal was present only in 2 spectra in the long TE sequence (as a negative doublet) and in 3 sequences of the short TE. In the latter sequence, identification of the Ala band may be impossible since it might be obscured by a neighbouring Lac-Lip signal. Although extension of the echo time (TE) helps to eliminate the lipid signal, it also evokes a negative band of Lac (1.33 ppm) which may again mask the Ala negative signal (1.48 ppm). Better separation of both signals can probably be achieved in MRS carried out in a magnetic field of greater magnitude [15]. It seems that the presence of Ala in meningiomas results from partial oxidation of glutamine, which takes place as part of an important metabolic pathway in these tumours [19].

There are reports stating that Glx is an important metabolite specific for meningiomas [15,20]. In the MRS spectrum, Glx forms two separate bands, β/γ-Glx and α-Glx. The first one has a broad bandwidth in the range 2.1-2.5 ppm and reflects presence of glutamine and glutamate. Another band in the position 3.8 ppm also contains information about glutathione (α-Glx/glutathione). The broad band width of β/γ-Glx makes its quantitative analysis quite difficult. For this reason, particular attention was given to the α-Glx signal, which in meningiomas forms a narrow and well-defined peak. Two studies reported significantly greater ratios of α-Glx/glutathione in meningiomas than in other cerebral neoplasms [15,21]. We were able to confirm these findings, as in our group it was possible to identify both

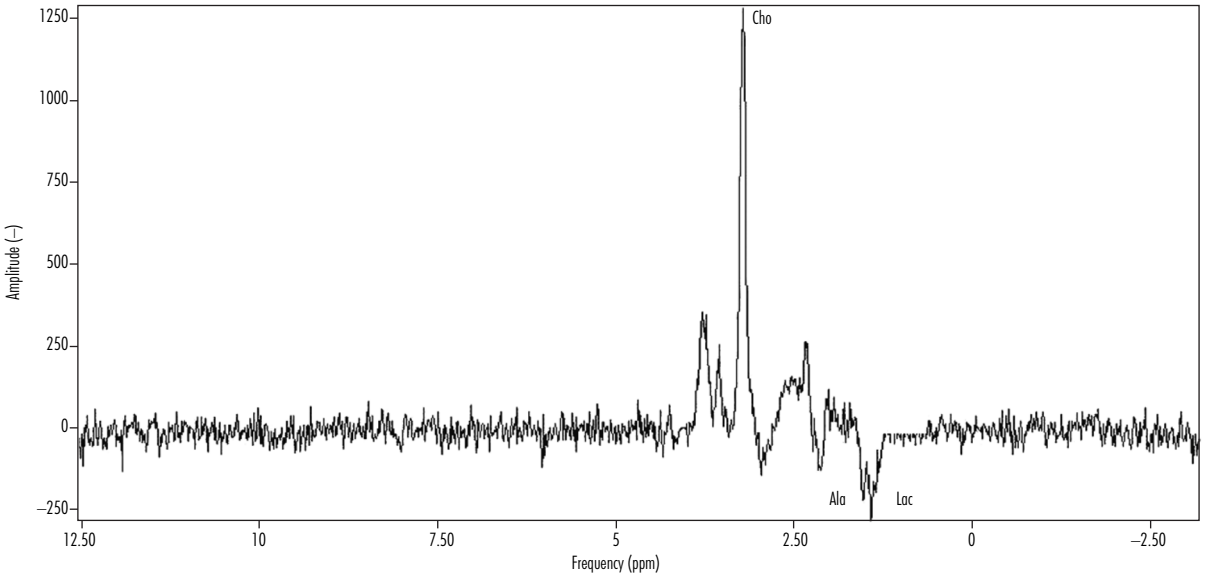

Fig. 2. Long-TE spectrum of meningioma

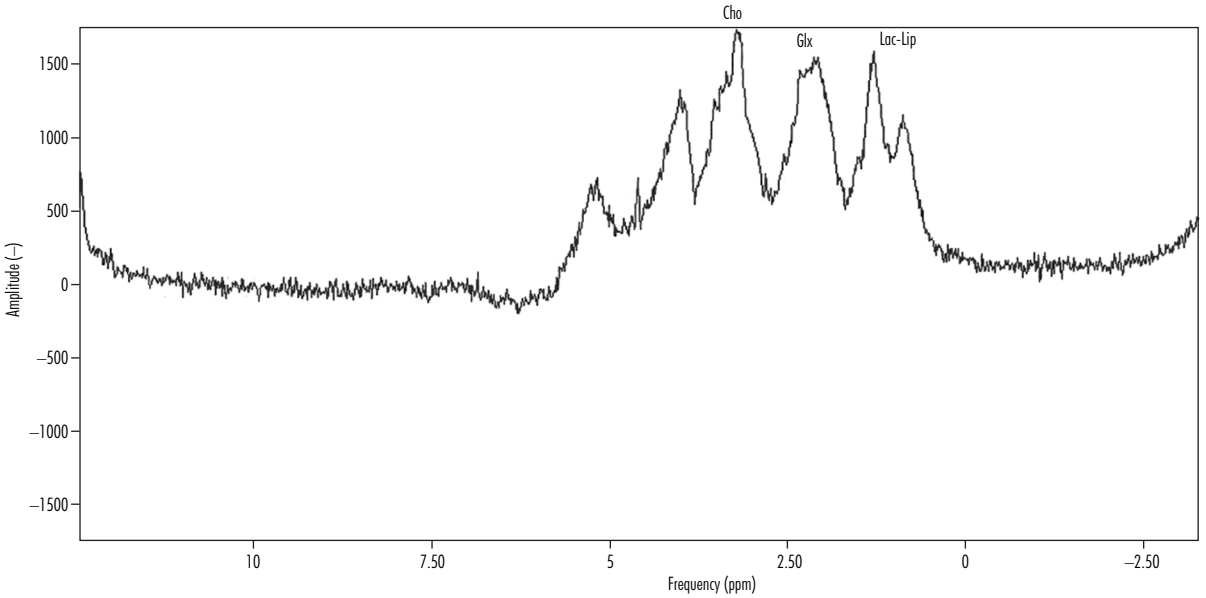

Fig. 3. Short-TE spectrum of meningioma

β/γ-Glx and α-Glx/glutathione signals in all 14 cases. Glutathione is a tripeptide consisting of glutamate, cystine and glycine. In its reduced form (GSH), this compound is an important antioxidant protecting cells against free radicals and peroxides. One study employing cytochemical methods revealed a significant decrease of GSH concentration in glioblastomas versus meningiomas and astrocytomas of WHO grade II [22].

The high concentration of GSH in WHO grade II astrocytomas could be responsible for their resistance against free radicals forming during radiotherapy and, consequently, might help explain their low susceptibility to systemic treatment [15]. Increase of GSH concentration may be a cause of the high contents of Ala and Glx as the metabolism of those compounds is linked together [13,15,17,18,21].

Apart from the information on metabolism, MRS may be of assistance in diagnosis in unusual clinical situations. A case of a 5-year-old boy operated on for anaplastic ependymoma in the fourth ventricle and subse-

quently receiving radiotherapy was reported [23]. Five years later, a follow-up MRI scan revealed a posterior fossa tumour which was thought to be either a recurrent ependymoma or a radionecrosis. However, an MRS suggested a meningioma and apparently this diagnosis was consistent with postoperative histopathology.

On the other hand, in a case of rarely occurring meningiomas with a necrotic zone (10-15% of all meningiomas) [24], which present on the scans as ring-enhancing lesions, MRS turned out to be of no value for diagnosis [25]. The spectrum shows only a high Lac-Lip signal which offers no assistance.

One study dedicated to diagnosis and distinction of benign (WHO grade I) and malignant (WHO grade II and III) meningiomas [16] claimed that a high Cho/Cr ratio and high Lac-Lip signals are specific for atypical and anaplastic tumours. Our study, as well as other ones [26], do not support this thesis. Among

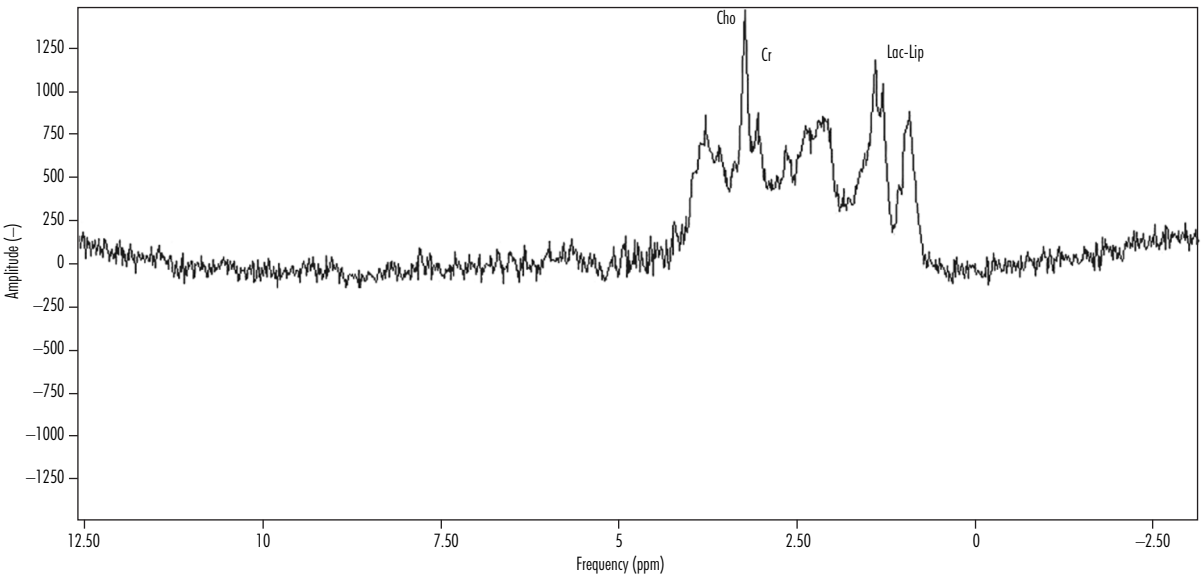

Fig. 4. Short-TE spectrum of cerebral lymphoma

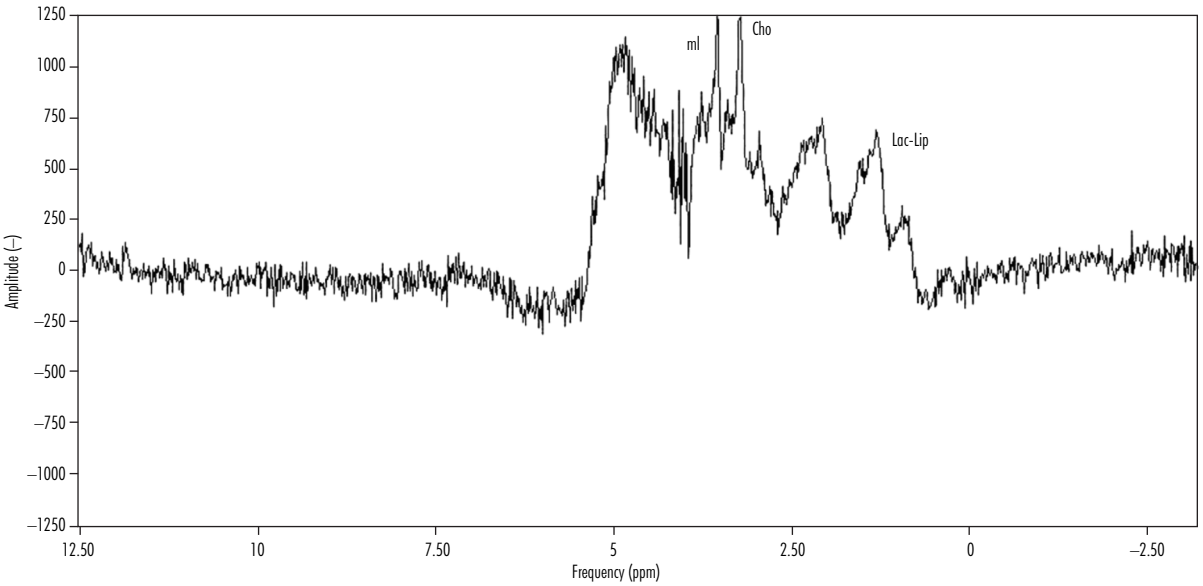

Fig. 5. Short-TE spectrum of vestibular schwannoma

4 patients with atypical meningioma (WHO grade II) and one with rhabdoid variant (WHO grade III), there was only a single instance of a high Lac-Lip signal. On the other hand, the Cho/Cr ratio was not calculated in those patients because of a total lack of Cr or only a very low band present. Consequently, in our material we were unable to distinguish low and high grade meningiomas.

According to a more recent study, the total concentration of alanine and creatine is significantly lower in high grade meningiomas (WHO grade II and III) compared to grade I tumours [27]. We could not verify these results since Ala peaks were absent in most of our spectra.

MRS appears to be useful in distinguishing meningiomas from lymphomas as both types of tumours look similar in MRI scans. In lymphomas, there are no signals characteristic for meningiomas, i.e., Ala and Glx (Fig. 4). In our material, the Glx band was present in

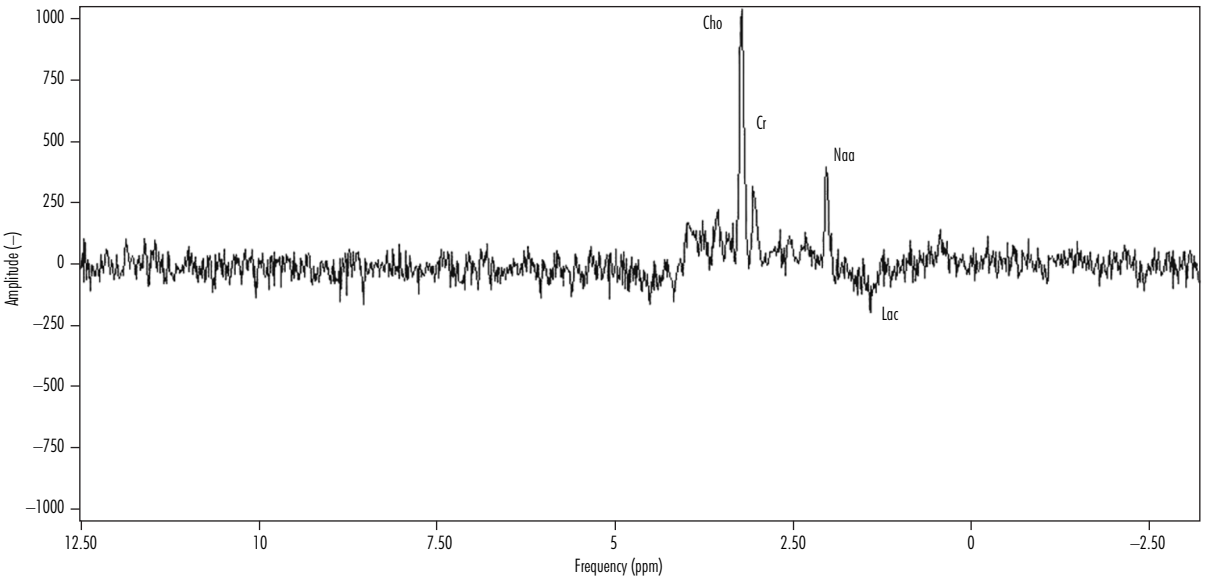

Fig. 6. Long-TE spectrum of haemangiopericytoma

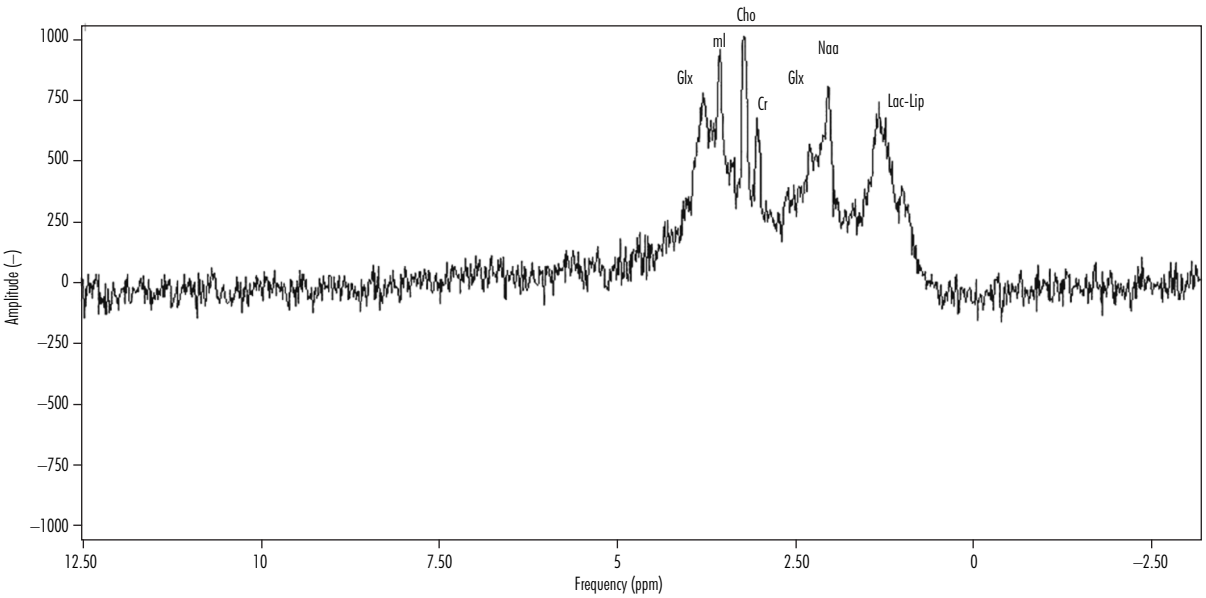

Fig. 7. Short-TE spectrum of haemangiopericytoma

all 14 patients with meningiomas and absent in both cases of lymphoma.

MRS could be of assistance to discriminate two of the most common tumours found in the cerebellopontine angle, i.e., meningiomas and vestibular schwannomas. In contrast to meningiomas, spectra of schwannomas acquired in the short TE sequences contain an apparent mI signal (Fig. 5). This feature, along with the lack of an Ala signal, allows differentiation of schwannomas from meningiomas [28,29].

Likewise, MRS seems to be helpful in diagnosing haemangiopericytomas, tumours that are virtually indistinguishable from meningiomas on MRI [30]. The haemangiopericytoma spectrum has the same characteristics as that of meningioma; however, there is no Ala signal, whilst a high mI peak is present [31] (Figs. 6 and 7). One study suggested that in cases of a low mI signal, the mI/Cho ratio should be calculated and a value greater than 0.9 warrants the diagnosis of haemangiopericytoma [31]. In our material, the very presence of an mI band sufficed to establish the correct diagnosis of haemangiopericytoma since it was never seen in the meningioma patients. Importantly, the Ala signal was absent in both our haemangiopericytoma cases.

Another study suggested that after preoperative embolisation of the feeding arteries, the meningiomas either reveal a previously absent Lac-Lip signal or this band is enhanced in comparison to pre-embolisation MRS [32]. These findings probably result from ischaemic injury of meningioma cells and tumour necrosis following embolisation [33].

Conclusions

1. In the majority of cases, MRI scans are sufficient to establish the appropriate diagnosis of meningioma. However, in case of doubt, in certain instances MRS can be helpful in preoperative distinction of meningiomas and other neoplasms of similar MRI appearance, particularly lymphomas (absent Glx signal), schwannomas (mI signal in the short TE sequences) and haemangiopericytomas (presence of mI band).
2. MRS is unable to discriminate low and high grade meningiomas.

Disclosure

Authors report no conflict of interest.

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