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Subtentorial primitive neuroectodermal tumors (PNET) – imaging diagnostics and MR spectroscopy

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Summary

Primitive neuroectodermal tumors (PNET) belong to embryonal tumors. They often comprise the highly malignant and invasive neoplasms of childhood. The classification of PNET includes medulloblastoma, the most important tumor of posterior fossa and supratentorial primitive neuroepithelial tumor, known as S-PNET. These tumors have a tendency to disseminate throughout CSF and cause subarachnoid metastases, which is associated with low survival rate.

We present epidemiologic, clinical and pathogenic aspects of these tumors groups. Computer tomography is the initial modality in diagnosis of PNET, but magnetic resonance imaging is of primary significance.

The information about MR spectroscopy application in patients with neuroectodermal neoplasms is scarce. Only in a few articles, based on MRS *in vitro* and *in vivo* studies, there was elevated concentration of taurine in spectra of PNETs. Literature data suggest, that MR spectroscopy has relevant value in differential diagnosis and could be useful in assessment of prognosis. In our article we attempt to review the literature concerning neuroectodermal tumors and take ours clinical cases into account.

Key words: primitive neuroectodermal tumors • PNET • magnetic resonance imaging • MR spectroscopy

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Background

Primitive neuroectodermal tumors (PNET) belong to the group of tumors of embryonal origin. They are childhood tumors with high grade IV histological malignancy, developing from undifferentiated or low-differentiated neuroepithelial cells with multidirectional transformation potential [1,2].

Classification of these tumors is unequivocal. However, tumors with sub- and supratentorial location can be distinguished (Table 1). Medulloblastomas are predominant among subtentorial tumors). Supratentorial lesions (S-PNET – supratentorial PNET) include blastic forms of pineal body tumors, tumors of the cerebral hemispheres (with cortical or subcortical localization), as well as lesions of the thalamus and suprasellar ones [3,4].

The peak of PNET diagnoses falls between 4 and 8 years of age, whereas up to 2 years of age such tumors are very

Table 1. Embryonal tumors according to Osborn AG et al. [6].

Embryonal tumors
Medulloepithelioma
Ependymoblastoma
Medulloblastoma (PNET-MB) – typical form – desmoplastic type – nodular type with high neuronal differentiation – gigantocellular type
Primitive neuroectodermal tumor (supratentorial) – (Supratentorial S-PNET)
Atypical teratoid/rhabdoid tumor (AT/RT)

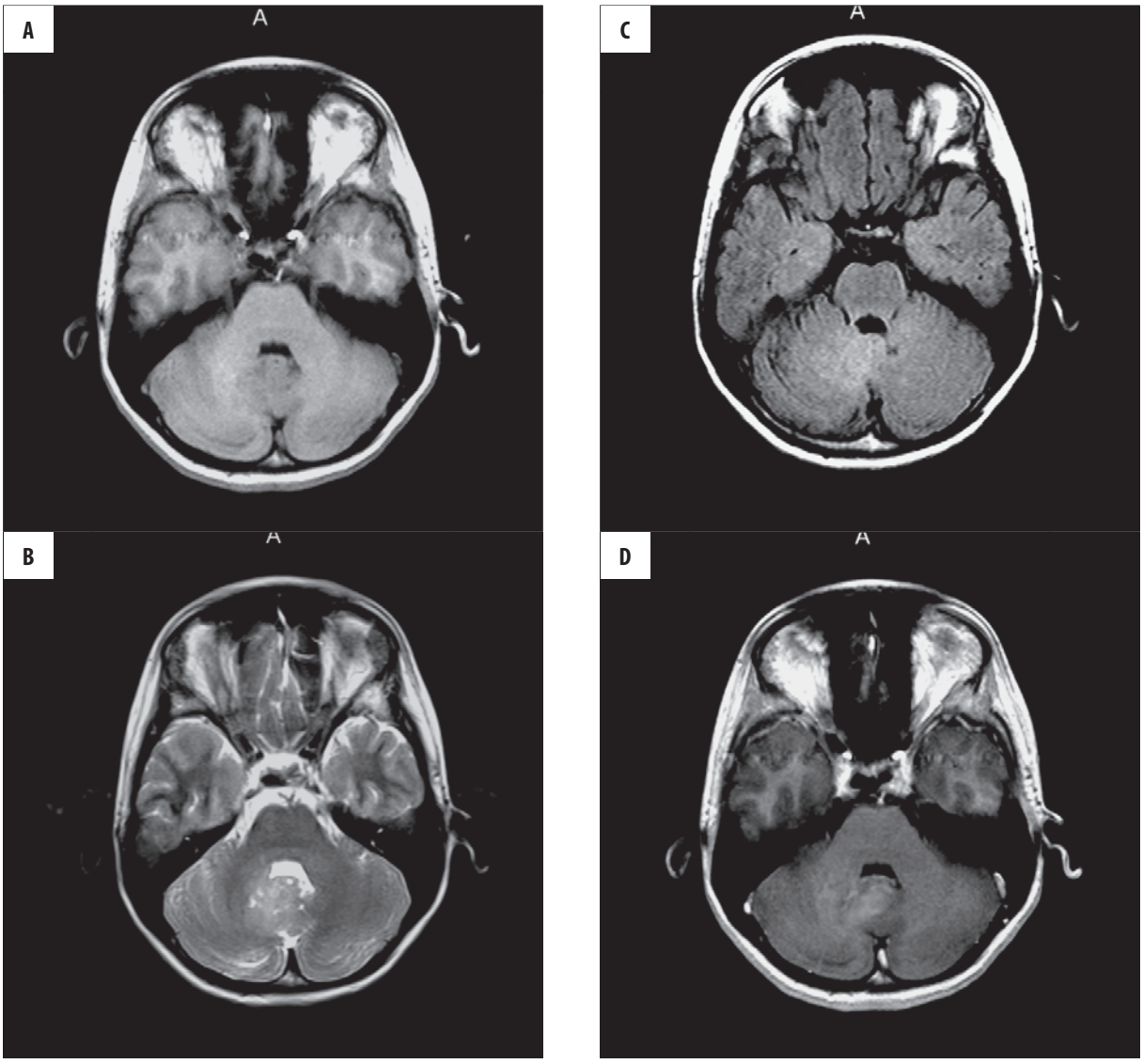


Figure 1. Histologically confirmed PNET in a 12-year-old child. Axial T1-weighted MR image (**A**). Axial T2-weighted MR image – high intensity tumor mass in the IV ventricle (**B**). FLAIR sequence demonstrates PNET tumors well (**C**). Heterogeneous enhancement of PNET after contrast administration (**D**).

rare and account only for 1–2% of all neoplasms [4]. Another peak of PNET diagnoses is observed between 20 and 24 years of age, as ca. 30% of these tumors become manifest in adults [5]. Subtentorial PNET occurs in 75% of cases below 10 years of age, but it is diagnosed most frequently at the age of ca. 5 years [6], whereas S-PNET is most often observed in younger children – 50% of these tumors become manifest below 5 years of age, and ca. 10% in the first year of life, but the mean age of diagnosis is 35 months [5,6]. Supratentorial tumors account for 1% of all CNS neoplasias and 5.6% of all primitive neuroectodermal tumors of the CNS [6]. The dynamics of growth in childhood is the reason for high malignancy and rapid growth rate of these tumors. In imaging studies, they are visualized as large heterogeneous lesions, often causing hydrocephalus. They also tend to infiltrate the cerebrospinal meninges and spread through the cerebrospinal fluid [7]. Distant metastases, most frequently to the bones, bone marrow, lymph nodes and liver are common [8].

Meduloblastoma, also referred to as PNET of the posterior cranial fossa (subtentorial PNET) belongs to the most frequent embryonal tumors (70% of cases). It constitutes 40% of all posterior cranial fossa tumors and 15–20% of all pediatric cerebral tumors [3,8]. It occurs in four forms: typical desmoplastic medulloblastoma, gigantocellular medulloblastoma, accounting for ca. 4% of cases, as a pigmented tumor type and a nodular type with highly differentiated neuronal structure, sometimes referred to as cerebellar neuroblastoma [6,8]. PNET is most often localized within the cerebellar vermis (ca 75% of cases), infiltrating the vault of the IV ventricle and the adjacent structure, which leads to rapid development of hydrocephalus. Usually the tumor is located in the medial line, filling the IV ventricle, but laterally located lesions spreading to the cerebellopontine angle are also described [3,8]. Lateral location is characteristic in older children and adults [6]. Laterally located lesions may cause connective tissue reaction, causing the growth of fibrous tissue in the vicinity of the tumor [5].

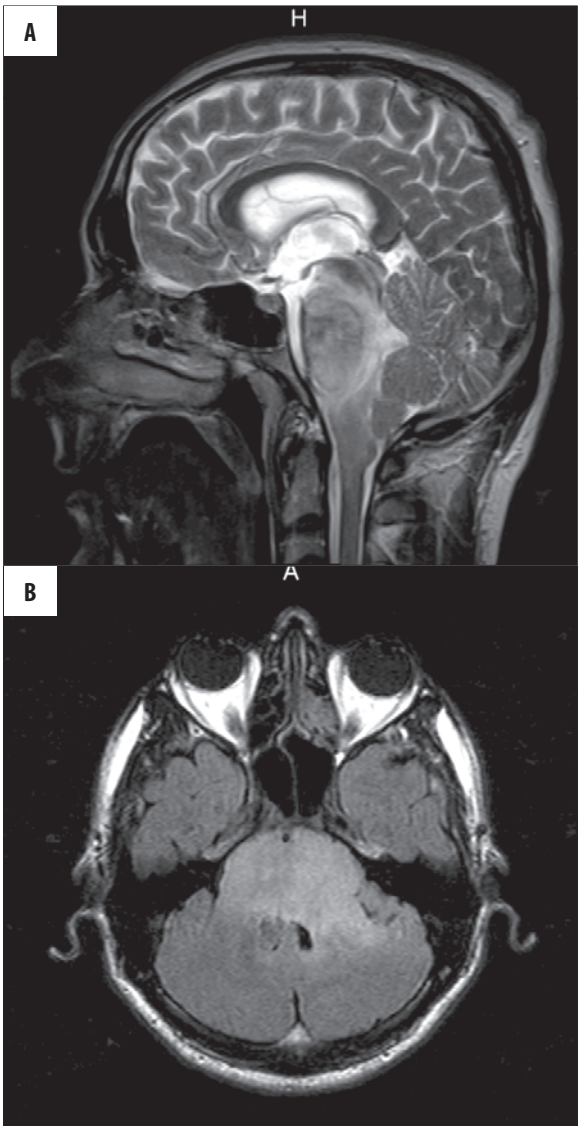


Figure 2. Inoperable pilocytic astrocytoma in a 26-year-old patient classified to radiotherapy. Hyperintense signal tumor localized in the brainstem and cerebellar peduncles in axial T2-weighted image (**A**) and in axial FLAIR sequence (**B**). No enhancement after gadolinium administration was observed (**C**).

Meduloblastomas reach reletively big sizes, even up to 1–3 cm [6].

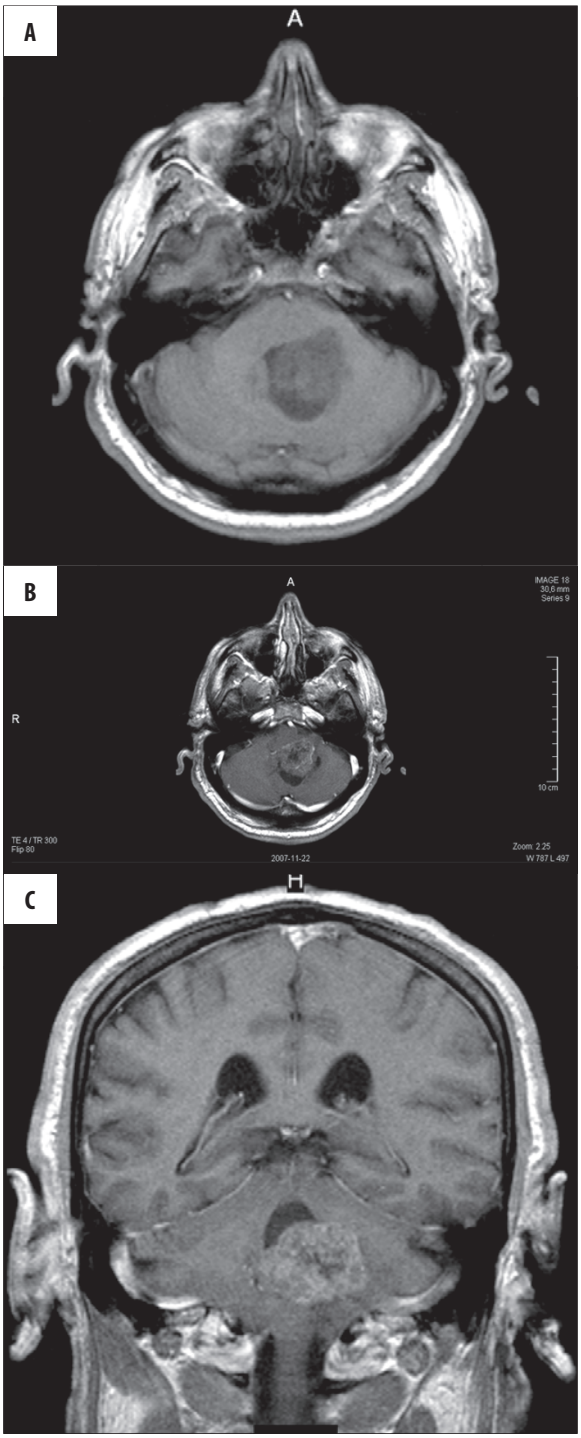
The literature emphasizes genetic factors determining the development of PNET type neuroectodermal tumors [1]. The described cytogenetic changes include structural aberrations in chromosome 17q (short arm loss), balanced translocation, presence of the suppressor gene TP53 as well as the PAX gene [6]. Many recent reports indicate a correlation between sporadic occurrence of medulloblastomas and a defect in the so-called Sonic Hedgehog (SHH) signaling system. Mutations of PTCH1 gene (within chromosome 9) and/or deletions of chromosome 9q elements associated with PTCH inactivation are observed in 30–40% of medulloblastoma. Additionally, mutations of the Suppressor of Fusem (SUFU) gene (10q24.3), which is a component of the SHH pathway, are also characteristic of this medulloblastoma variant and may have prognostic significance [1]. The presence of this tumor can be associated with such syndromes as Gorlin, Li-Fraumeni, Turcot, Gardner, Bowden syndrom and ataxia-telangiectasia syndrome (Louis-Barr disease) [5,6].

PNET is usually a highly malignant and invasive tumor [6]. Its microscopic structure presents densely packed, hyperchromatic cells with pale cytoplasm, characterized by high nucleus to cytoplasm volume ratio, high mitotic index and neurono-neuroblastic differentiation manifested by formation of Homer-Wright rosettes [9,10].

As far as imaging studies are concerned, CT visualizes it as a hyperdense, homogeneous tumor, usually oval in shape and well-delineated. In 20% of cases, it contains calcifications, in 40–50% – cystic and necrotic lesions. Hemorrhagic lesions, iron and melanin deposits as well as fibrous areas can be seen. After contrast administration, the tumor undergoes considerable, relatively homogeneous enhancement, with no enhancement in the areas corresponding to cysts and necrosis [3–6].

In MR, in T1-weighted images, PNET is a tumor hypointense in comparison with the gray matter, in T2-weighted images iso- or hyperintense (Figure 1A,B). The FLAIR sequence is also useful in MR imaging, as it allows to visualize the tumor well on the background of cerebrospinal fluid in the IV ventricle (Figure 1C). After contrast administration, PNET is significantly, often inhomogeneously enhanced (Figure 1D). Wilke et al. [11] believe that the decrease of ADC value in diffusion studies reflects small-cell texture of the tumors and is charActeristic of PNET, whereas Schneider et al. [12] suggest that combined DWI and MRS techniques allows to differentiate posterior cranial fossa tumors in children – among others, PNET, ependymoma, pilocytic astrocytoma. Positron emission tomography (PET) with the use of FDG, 11C-methionine and 11C-choline can also be useful [13].

Differential diagnostics of subtentorial PNET folms should take into consideration astrocytomas – pilocytic



(Figure 2A–C) and hairy cell astrocytoma, which is a cystic tumor with nodular contrast enhancement [6]. In older children also ependymoma should be considered – an inhomogeneous tumor with calcifications and hemorrhagic areas (Figure 3A–D) [6]. Differential diagnostics also takes into account papilloma located in the IV ventricle, showing strong and homogeneous contrast enhancement with less significant mass effect [6]. Since atypical PNET forms occur particularly often in adults, PNET should always be considered in differential diagnostics of posterior cranial fossa tumors [14].

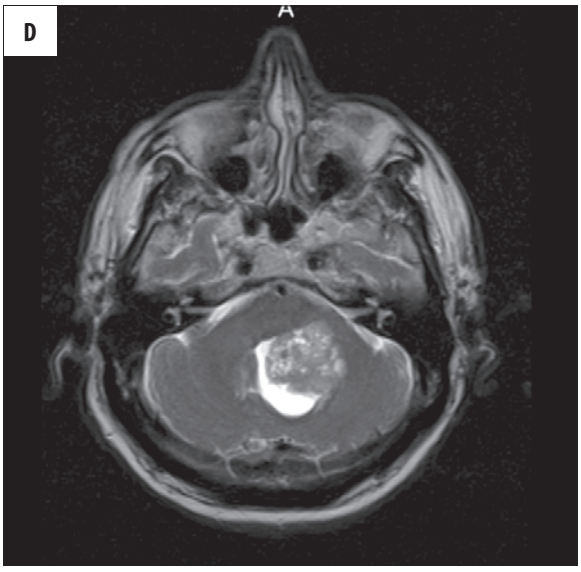


Figure 3. Histologically proven ependymoma of the IV ventricle in a 71-year-old patient. Axial T1-weighted image before (**A**) and after administration of gadolinium – axial (**B**) and coronal plane (**C**). Hypointense signal tumor with strong, irregular enhancement. Heterogeneous signal intensity of the tumor in T2-weighted image (**D**).

If a PNET is suspected, contrast administration is necessary to detect metastatic foci in the spinal canal as a result of spread through CSF [2,3,6,15]. Metastases in the subarachnoid space are found in 50% of cases, therefore if there is a suspicion of PNET it is recommended to extend the diagnostics and to examine the spinal canal as well [3,15].

Clinical symptoms are early and may include ataxia, dizziness, increased intracranial pressure, cranial nerve palsy. On physical examination, papilloedema on the eye fundus, nystagmus, dysdiachokinesia or hypotonia can be observed. In case of spinal PNET location, the patient can experience nuchal pain, pain and weakness of the lower extremities, impairment of intestinal and cystic function, leading to urinary incontinence [6,8].

The aim of surgical treatment of PNET is to remove the tumor and to restore normal CSF flow. The effectiveness of chemo- and radiotherapy, also in younger children, has been demonstrated. However, radiotherapy can be used only in children above 3 years of age [16,17]. The factors determining effectiveness of the therapy include: age (below or above 3 years of age), tumor size (smaller or larger than 1.5 cm^2), brain stem involvement and/or the presence of metastases in imaging studies or CSF cytology [8].

The 5-year survival rate amounts to 80–85% [6]. Such a low index is due to the fact that PNET shows a tendency to relapse, even a case of late relapse 21 years after resection of the primary tumor has been described [18].

MR spectroscopy

There are only a few reports concerning MR spectroscopy performed in PNET patients. These tumors, just like other CNS neoplasms, are characterized in 1H MRS spectra by

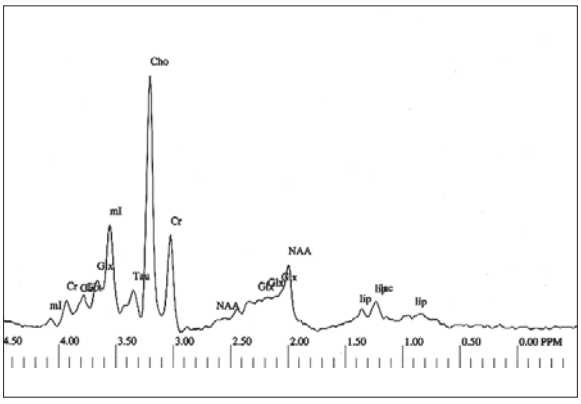


Figure 4. MR spectroscopy shows decreased N-acetylaspartate level, increased concentration of choline and a peak of taurine in histologically proven PNET in a 12-year-old child.

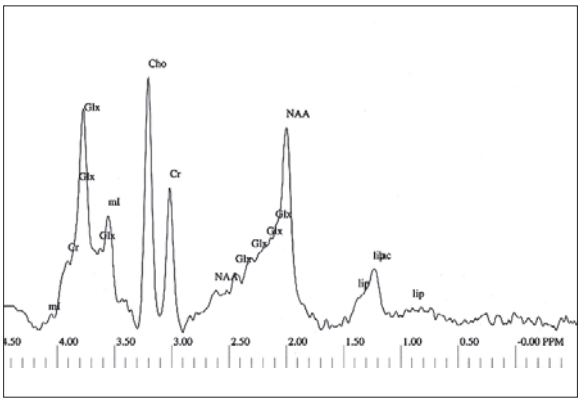


Figure 5. Spectrum of pilocytic astrocytoma during radiotherapy shows slight decrease in N-acetylaspartate level and increased concentration of choline compounds. Increased glutamine/glutamate ratio and marked elevation of lactates as a result of radiotherapy.

reduced NAA content and elevated choline [5]. Such changes of metabolite content in case of PNET patients were observed, among others, by Chawla et al. and Tugnoli et al. [15,19]. High choline content is associeted with tumor structure with densely packed cells and increased membranous structure transformation. Majos et al. [20] state that a characteristic feature of PNET in MRS spectra is also the lack of lipid bands, which distinguishes PNET among other highly malignant tumors such as glioblastomas.

Additional information concerning the metabolic profile of PNET were obtained from *in vitro* studies using high resolution MR spectroscopy. Tugnoli et al. [19] detected increased concentrations of myoinositol, taurine and phosphorylethanolamine – a component of choline band, whereas Sutton et al. [21] observed in 9 PNET cases the presence of glycine, taurine and inositol bands and considerable increase of choline content (Cho/NAA), with less marked increase of glutamate/glutamine proportion. A significant increase of taurine content in such tumors was also demonstrated by Kinoshita et al. [22].

The presence of a taurine band in a medulloblastoma patient in 1H MRS performed *in vivo* was first described by Wilke et al. [11]. Majos et al. [20] demonstrated increased taurine levels in adult patients with PNET. The presence of this compound in 3 PNET patients was also observed by Chawla et al. [15], and the presence of a taurin band in PNET spectra are confirmed by observations of Japanese authors [23].

Taurine, 2-aminoethanosulfonic acid, is an organic compound commonly regarded as an amino acid, although it does not have a carboxyl group. It is involved in metabolism of bile acids in the liver and in creatine transport in skeletal muscles. It is also present in the CNS, where it is involved in osmotic processes and probably plays a role of a neurotransmitter inhibiting the dopaminergic system [24]. In normal CNS, taurine is present in the cerebellum, Purkinje cell bodies, short neuronal projections, Golgi axial fibers, cerebellar cortex basket cell axon terminals and neuroglia processes [25–27]. Crabai et al. found high taurine levels in normal pineal body, pituitary and retina [28]. Flint et al. [29] demonstrated considerable concentrations of taurine in the developing cerebellum and the neocortex.

Age-related changes of taurine content in different periods of brain development were described by Pouwels et al. [30] and Kreis et al. [31].

Assessment of taurine content in *in vivo* MRS studies is difficult because of its low content in the brain and partial overlap between the taurine band and the signals of other compounds, such as scillo-inositol or glucose. However, more advanced techniques of MR spectroscopy allow even quantitative measurements of taurine content [30,31].

The largest clinical study concerning this problem included 13 patients [32]. In all the cases, increased taurine content was found in *in vivo* MRS, which was also confirmed in high-resolution spectroscopy. The authors of the report suggest that high content of this compound is highly pathognomonic for PNET type tumors.

Both the presence of taurine band and other spectroscopic features such as significant depletion of NAA, markedly increased concentrtion of choline compounds and the lack of lipid bands make up the spectroscopy standard for PNET (Figure 4). Thus, MR spectroscopy contributes some important elements to differential diagnostics when PNET is suspected, which is confirmed by comparative analysis of different subtentorial tumor spectra performed by Majos et al. [20] (Figure 5). On interpretation of the spectra, however, it should be remembered that taurine level can also be increased in other embryonal tumors, e.g. of the pineal body, or in highly malignant astrocytomas [32,33].

Spectroscopic data can also provide a clue for consideration of the origins of neuroectodermal tumors. Such conclusions can be drawn from the study by Florian et al. [34], who found on the basis of *in vitro* spectroscopic studies that NAA expression in PNET cells correlates negatively with their neuronal differentiation, which may indicate that these cells originate from precursor cells with type 2 oligodendrocytic phenotype. On the other hand, increased level of taurine, a compound present in high concentration in immature brain, observed in PNET spectra, undoubtedly confirms that the tumor originates from primitive and undifferentiated neural cells [31].

Spectroscopy seems also to be potentially useful in prognostic assessment. Peet AC et al. [35] demonstrated, that MRS metabolic profiles allow to differentiate PNET forms associated with high risk of metastases from limited, well-delineated forms. Dembowska-Bagińska et al. [36] believe that metabolite levels assessed in MR spectroscopy correlate significantly with the course of thr disease and the instituted chemotherapy, whereas Peeling et al. [33] suggest that taurine content may correlate with tumor malignancy, and quantitative measurements of taurine in MR spectroscopy *in vivo* may have prognostic value.

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