Infratentorial pediatric brain tumors: the value of new imaging modalities

Tumeurs de la fosse postérieure de l’enfant : apport des techniques d’imagerie avancées

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KEYWORDS
Brain; Cerebellum; Tumors; MRI; Diffusion; Spectroscopy; Children

Abstract The correct assessment of the four most frequent infratentorial brain tumors in children (medulloblastoma, ependymoma, pilocytic astrocytoma and infiltrating glioma) has always been problematic. They are known to often resemble one another on conventional magnetic resonance (MR) imaging. We tested the hypothesis whether the combined strength of diffusion-weighted imaging (DWI) and proton MR spectroscopy (MRS) could help differentiate these tumors. Seventeen children with untreated posterior fossa tumors were investigated between January 2005 and January 2006 with conventional MR imaging and combined DWI and MR spectroscopy using a single-voxel technique at short and long echo time (TE) of 30 ms and 135 ms respectively. Apparent diffusion coefficient (ADC) values were retrieved after regions of interest were manually positioned within non necrotic tumor core. Water signal was quantified and metabolite signals were compared and analyzed using linear discriminant analysis. When a combination of ADC values and normalized metabolites was used, all tumors could be discriminated against one other. This could only be achieved when metabolites were normalized using water as an internal standard. They could not be discriminated when using metabolite ratios or ADC values alone, nor could they be differentiated using creatine (Cr) as an internal reference even in combination with ADC values. In conclusion, linear discriminant analysis and multiparametric combination of DWI and MRS, although not replacing histology,
Introduction

Magnetic Resonance Imaging (MRI) is the most important tool in the early evaluation of primary brain tumors in children. Choice of treatment, long-term prognosis as well as quality of life in survivors, are all dependent on a correct initial diagnosis. However, conventional MRI is often limited in identifying specific tumor types and cannot reliably differentiate between high-grade and low-grade lesions. Histopathologic evaluation of brain biopsies still is the gold standard for definitive diagnosis. Therefore, there is a need to gather additional information prior to any therapeutic decision, especially in cases where a tumor biopsy cannot be done.

Diffusion-weighted imaging (DWI) allows evaluation of the rate of microscopic water diffusion within tissues. It is used to distinguish necrosis from cyst formation or edema and has shown some efficiency in identifying different tumor types and delimiting their boundaries against normal cerebral tissue [17,25,30]. Proton magnetic resonance spectroscopy (MRS) analyzes the metabolic activity and chemical composition of the tissue studied through several spectra recorded at short echo time (TE) of 30 ms and long TE (TE = 135 ms). The values of coefficients of diffusion apparente (ADC) have been obtained from different regions of interest placed at the center of the non-necrotic part of the tumor. The signal of the water was quantified in all cases. A linear discriminant (LDA) method on components principal uses signa metabolites such as values of ADC, engender a complete separation of the four groups tumors. This separation was not obtained when using only normalizing metabolites by water signal or with creatine (Cr) not permitting a complete separation of the tumors. In conclusion, the combination of diffusion-weighted imaging (DWI) and MRS was shown not to replace a histological diagnosis, but permits an identification with certainty, within a pediatric population, the four tumors that the most frequent from the posterior fossa, to condition that the metabolites used were normalized using water signal as an internal reference.

Studies that have used DWI and MRS together to analyze brain tumors are scarce [35,37,40]. Thus, the purpose of our study was to determine if the combination of both techniques could help differentiating the most frequent posterior fossa tumors in children.

Materials and methods

We retrospectively studied 17 patients with a diagnosis of posterior fossa tumor. The mean age of the patients was 8.2 years (+5.3 SD), there were 13 male and 4 female patients. All patients underwent DWI and MRS as part of our institutional protocols, no additional consent was necessary. Children were examined at initial presentation and before any surgical or adjuvant therapy. In all cases, children were operated upon and tumor specimens were reviewed by an experienced neuropathologist (DFB) after surgical resection (Table 1).

All MR examinations were performed on a 1.5 Tesla Symphony Maestro Class (Siemens Medical Systems, Erlangen, Germany) using a circularized polarized head coil. MRS obtained by the single voxel technique, was performed after the standard MRI protocol and the spectra were acquired using a spin echo sequence (PRESS) with short and long echo times (TE) of 30 ms and 135 ms respectively. The size of the nominal volume of interest (VOI) was 4.5 cm³ (20 × 15 × 15 mm³) and was placed within the solid portion of the tumor lesion avoiding necrotic areas, calcifications, cysts or hemorrhagic foci. Sequences were performed with water saturation. The MRS parameters for PRESS spectra recorded at short TE (30 ms) were as follows:

fully discriminates the four most frequent posterior fossa tumors in children, but metabolites have to be normalized using water and not Cr signal as an internal reference.
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Résumé Les quatre tumeurs infratentorielles les plus fréquentes chez l’enfant (médulloblastome, épendymome, astrocytome pilocytique et gliome infiltrant) restent d’un diagnostic délicat. L’examen en résonance magnétique nucléaire (RMN) conventionnel ne permet souvent pas de poser un diagnostic exact avec certitude. Nous avons tenté de déterminer si l’utilisation conjointe de l’imagerie de diffusion (DWI) et la RMN spectroscopique (MRS) pouvait aider à les différentier. Entre janvier 2005 et janvier 2006, 17 enfants porteurs d’un diagnostic de tumeur de la fosse postérieure furent investigués par DWI et MRS, en utilisant une technique de single voxel en écho court (TE) de 30 ms et écho long (TE = 135 ms). Les valeurs des coefficients de diffusion apparente (ADC) ont été obtenues à partir des régions d’intérêt placées au centre de la partie non nécrosée de la tumeur. Le signal de l’eau fut quantifié dans tous les cas. Une analyse discriminate lineaire en composants principaux utilisant les signaux des métabolites ainsi que les valeurs d’ADC, engendra une séparation complète des quatre groupes tumoraux. Cette séparation ne fut obtenue qu’avec une normalisation des métabolites par rapport au signal de l’eau. Ni l’utilisation des valeurs d’ADC ou des métabolites seuls, ni une normalisation des métabolites par rapport au créatine (Cr) ne permirent une séparation totale des tumeurs. En conclusion, l’analyse discriminate lineaire et la combinaison multiparamétrique du DWI et MRS, bien que ne remplaçant pas un diagnostic histologique, permettent d’identifier avec certitude, dans une population pédiatrique, les quatre tumeurs les plus fréquentes de la fosse postérieure, à condition que les métabolites utilisés soient normalisés par rapport au signal de l’eau.
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TR = 1500 ms, 64 scans, total acquisition time of 1 min 36 s, and at long TE (135 ms): TR = 1500 ms, 85 scans, total acquisition time of 2 min 07 s respectively. In all cases, water signal was acquired and its signal intensity measured. After zero filling and exponential filtering, the PRESS data were fitted in the time domain using a metabolic database derived from MRS acquisitions of aqueous model solutions of pure metabolites using the AMARES-MRUI FORTRAN code [33] included in a homemade software developed under IDL environment (Iterative Data Language, Research System Inc., Boulder, CO). Metabolite signals were hence measured and normalized using water signal intensity as an internal reference.

DW imaging was performed with axial multi-slice multi-repetition spin-echo echo-planar technique (TR = 3600 ms, TE = 107 ms, slice thickness = 5 mm, three averages per image, field of view = 240 × 240 mm, 128 × 128 acquisition matrix). Diffusion was measured in three orthogonal directions at two values of b (b=500 s/mm² and 1000 s/mm²). An additional set of images was obtained with no diffusion weighting. The total acquisition time for the DWI was 51 s. DW images and the averaged apparent diffusion coefficient (ADC) maps were automatically generated using Siemens software. DWI and ADC data were subsequently transferred to a workstation using IDL software for further analysis. A single sized region of interest (ROI) of 45 mm² was placed

<table>
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<tr>
<th>Patient</th>
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<th>Age</th>
<th>Histological diagnosis</th>
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<td>1.9</td>
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<td>Ependymoma grade II</td>
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<td>Pilocytic astrocytoma</td>
</tr>
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Table 1 Age repartition in years and histological diagnosis in all patients

Figure 1 Axial T2-wi of a medulloblastoma (A), ependymoma (B), infiltrating glioma (C), pilocytic astrocytoma (D).

Figure 1 Images axiales en pondération T2 dans le cas d’un medulloblastome (A), ependymome (B), gliome infiltrant (C), astrocytome pilocytique (D).
within the solid core of tumoral tissue and ADC values retrieved.

**Statistical analysis**

Correlation analysis and non parametric Spearman’s rho test were used to compare the MR parameters among tumor categories. Non parametric Wilcoxon / Kruskal-Wallis rank tests were used to compare tumor groups against one another, with respect to median values of normalized metabolites detected at short TE, and ADC values. Linear discriminant analysis using ADC values and normalized levels of metabolites as variables of principal components analysis was performed. This procedure using a generalized distance measure allows the definition of regions in a canonical space based on possible predicting variables, and to predict whether a tumor with its particular values in one specific region is likely to belong to a specific type. Statistical analysis was conducted with the JMP software (JMP IN, Version 5.1.2, SAS, Cary, NC, USA).

**Results**

Figs. 1-5 illustrates the four studied tumors medulloblastoma (M), ependymoma (E), infiltrating glioma (G), pilocytic astrocytoma (PAC). Comparison of spectra obtained at short (TE=30 ms) and long (TE=135 ms) echo time of MRS.

**Figure 2** Short and long echo time MRS of a medulloblastoma (same patient as in Fig. 1a). Notice the low NAA and Cr signal and the elevated level of Tau at 3.4 ppm. The small medallion inserted in the frequency shift axis shows the scaled spectrum of Tau from a model solution of the pure metabolite at pH=7, acquired at 1.5T.

**Figure 3** Short and long echo time MRS of an ependymoma (same patient as in Fig. 1b). Notice the high levels of mI and very low levels of NAA and Cr.

**Figure 4** Short and long echo time MRS of an infiltrating glioma (same patient as in Fig. 1c). Spectrum shows high levels of mI, and slightly decreased levels of NAA and Cho.

**Figure 5** Short and long echo time MRS of a pilocytic astrocytoma (same patient as in Fig. 1d). Notice the moderately low NAA and Cr peak as well as the presence of Lactate (Lac).
tic astrocytoma (PA) and their related spectra (Figs. 1-5) at short TE (30 ms) and long TE (135 ms). It shows how conventional imaging fails short of appropriately labeling a tumor in the posterior fossa in a child. All four cases demonstrate an essentially round-shaped tumor located within the boundaries of the fourth ventricle, with a high intensity on T2-weighted images. All examinations showed otherwise intermediate to low signal intensity on T1-weighted image, and variable contrast enhancement within the solid portions of the tumor itself (not shown).

Linear discriminant analysis with seven variables including ADC values and six normalized metabolites (using water signal as an internal reference) demonstrates a complete separation of all tumor groups with a predictive value of 1 in all cases (certainty), a \(-2\text{LogLikelihood} < 1 \times 10^{-9}\) and no misclassification (Fig. 6). This full differentiation was not achieved by using either ADC alone or any combination of metabolites ratios. When using Cr as an internal standard, although discriminant analysis was still able to classify tumors correctly, the statistical overall positive predictive probability was much lower, with a \(-2\text{LogLikelihood} = 3.519\)

**Figure 6** Canonical Plot for medulloblastoma (○), ependymoma (●), infiltrating glioma (*), pilocytic astrocytoma (+). The size of the circles corresponds to the 95% confidence limit for each of the group mean. The central straight lines represent the biplot rays which are the seven variables in the principle component analysis (or JK’ principal component biplots). The central point of corresponds to the grand mean of all groups. All tumors were correctly classified with a predictive probability of 1 and a \(-2\text{LogLikelihood} < 1 \times 10^{-9}\).

**Figure 7** Same canonical plot as in Fig. 6, but all metabolites are normalized using Cr as an internal standard. All tumors were still correctly classified but with a lower predictive value in all cases (not shown), the \(-2\text{LogLikelihood} \approx 3.519\). Medulloblastoma (○), ependymoma (●), infiltrating glioma (*), pilocytic astrocytoma (+).

**Résumé**

Les tumeurs pédiatriques infratentoriales : la valeur de nouvelles modalités d’imagerie. L’analyse discriminante linéaire avec sept variables, y compris les valeurs d’ADC et six normales métabolites (avec la signal d’eau comme référence interne) démontre une séparation complète de tous les groupes de tumeurs avec une valeur prédictive de 1 dans tous les cas (certitude), une \(-2\text{LogLikelihood} < 1 \times 10^{-9}\) et aucune méconnaissance (Fig. 6). Cette différenciation complète n’a pas été réalisée en utilisant seul l’ADC ou toute combinaison de métabolites. Lorsqu’on utilise Cr en tant qu’témoignage interne, bien que l’analyse discriminante ait encore pu classer les tumeurs correctement, la probabilité statistique globale de prédiction positive a été beaucoup plus faible, avec un \(-2\text{LogLikelihood} = 3.519\).

**Figure 7** Représentation dans l’espace canonique des médulloblastomes (○), épendymomes (●), gliomes infiltrants (*), astrocytomes pilocytiques (+). La taille des cercles correspond à 95 % de la limite de confiance pour la moyenne de chaque groupe. Les lignes centrales sont les rayons biplans qui représentent les sept variables de l’analyse en composants principaux (composants principaux biplans de JK). Le point où les lignes biplans se recoupent correspond à l’emplacement de la moyenne des moyennes. Toutes les tumeurs sont correctement classifiées avec une prédiction de 1 (certitude) et une valeur de -2 LogProbabilité < 1 \times 10^{-9}.
as shown in Fig. 7 (specific probability for each tumor and predicted tumor classification not shown).

Analysis of biplot rays (the variables in the principle component analysis) demonstrates that the main variables which were able to isolate M from all other tumors consist of a combination of elevation of Tau and Cho levels, and a reduction in ADC values. This finding is further confirmed by a Wilcoxon / Kruskal-Wallis rank test showing highly significant median differences in normalized levels of Cho ($p = 0.0021$), Tau ($p < 0.001$) and ADC values ($p < 0.001$), between M and the other three posterior fossa tumors (Fig. 8a–c).

G and E as a group could be adequately discriminated from PA and M together, by an elevation in ml levels (Fig. 9). This was also confirmed by a Wilcoxon / Kruskal-Wallis rank test showing significant median differences in normalized levels of ml in G and E, compared to PA and M ($P=0.023$).

Selected examples of relationships of the parameters examined in this study are shown in Fig. 10. This figure illustrates the relationships between Tau versus Cho (a), ADC versus Tau (b), ADC versus Glx (c), and ADC versus Cho (d). Tau and Cho showed a significant positive correlation ($p < 0.001$, Fig. 6a), whereas the relationship between

![Figure 8](image-url)

**Figure 8** Box plots illustrating that ADC values (a), normalized values of Taurine (Tau) (b) and Choline (Cho) (c) differentiate medulloblastoma (M) from the other three posterior fossa tumors (PA: pilocytic astrocytoma, G: infiltrating glioma, E: ependymoma). The limits of the box represent the lower quartile (25th percentile) and upper quartile (75th percentile); the length of the box height is the interquartile range. The top and bottom whiskers are the maximum and minimum value. The line dividing the box is the median. a) A significantly lower ADC is observed in the medulloblastoma (median 0.816; min 0.554; interquartile range 0.712–0.881; max 0.976) versus all other tumors (when pooled together: median 1.282; min 0.87; interquartile range 1.036–1.656; max 2.121) $p < 0.001$, Wilcoxon/Kruskall-Wallis test. b) A significantly higher median Tau is observed in the medulloblastoma (median 0.249; min 0.141; interquartile range 0.146–0.381; max 0.476) versus all other tumors (when pooled together: median 0.059; min 0.00; interquartile range 0.026–0.089; max 0.112) $p < 0.001$, Wilcoxon/Kruskall-Wallis test. c) A significantly higher Cho is observed in the medulloblastoma (median 0.807; min 0.573; interquartile range 0.602–1.009; max 1.555) versus all other tumors (when pooled together: median 0.408; min 0.287; interquartile range 0.315–0.576; max 0.74) $p = 0.0021$, Wilcoxon/Kruskall-Wallis test.
Figure 9  Box plots illustrating that normalized myo-Inositol (mI) values differentiate ependymoma (E) and infiltrating glioma (G) from pilocytic astrocytoma (PA) and medulloblastoma (M). The limits of the box represent the lower quartile (25th percentile) and upper quartile (75th percentile); the length of the box height is the interquartile range. The top and bottom whiskers are the maximum and minimum value. The line dividing the box is the median. A significantly higher mI is observed in the E and G (median 0.635; min 0.246; interquartile range 0.312–0.856; max 0.911) versus M and PA (median 0.178; min 0.01; interquartile range 0.142–0.287; max 1.144) \( p = 0.023 \), Wilcoxon/Kruskall-Wallis test.

ADC and all three metabolites (Tau, Glx and Cho) were negative (all \( p < 0.05 \), Fig. 6b–d).

Discussion

\(^1\)H-MRS and DWI provide bio- and physicochemical information that cannot be obtained with conventional imaging techniques alone. Previous reports have demonstrated the ability of MRS to improve differentiation among tumors or even to identify specific histological tumor types \([4,38,41]\). These results have mainly been acquired at long echo time (TE 130 ms or longer) \([11]\) and only recently, MRS data obtained at short echo time (with a TE of 35 ms or less) have been published \([32,41]\). On the other hand, several reports have shown that ADC values could be used to differentiate some tumors \([2]\) or evaluate their cellularity \([10]\). Thus, an approach combining both spectroscopic and diffusion imaging techniques has become obvious in the field of brain tumors. We were interested in examining whether MRS and DWI together could provide us a better input and guide preoperative decisions in case of pediatric posterior fossa brain tumors.

The evaluation of brain tumors by means of MRS has mainly relied upon more or less sophisticated metabolite ratios (such as NAA/Cho, NAA/Cr, Cho/Cr, or NAA/(Cho +Cr) among others), sometimes using controlateral measurements for comparison. The use of a ratio is ambiguous when both terms are varying simultaneously. Moreover, ratios’ evaluation using Cr or Cho as an internal reference, bear an implicit bias as it is assumed that the denominator does not vary, which is at least questionable when addressing different tumors’ histology. A study of untreated pediatric brain tumors demonstrated a significant reduction of total Cr concentration in pediatric brain tumors \([15]\). This prompted us to measure and normalize each compound e.g. mI, Tau, Cho, Cr, NAA, by using water signal intensity as an internal standard, the acquisition of tissue water signal being acquired in a very short time. We focused exclusively on the non necrotic lesion core and excluded all cystic or necrotic components when positioning the measurement’s voxel, obviating the need for segmentation analysis. Single-voxel acquisition method was selected instead of chemical shift imaging to ensure that the quality of the spectrum (including magnetic field homogeneity and water suppression) was optimal. Correction factors for T1 saturation and T2 relaxation were omitted, as was the variation of water content of individual tumors. We assumed that the latter did not affect the validity of the findings, considering the variation to be very small in comparison with metabolite variations \([27]\).

Linear discriminant analysis has been demonstrated a powerful tool in classifying tumors. Indeed, in the study by Tate et al. \([18]\), differentiation between supratentorial adult tumors, including meningiomas, low-grade astrocytomas and aggressive tumors like glioblastomas and metastases was successful in 96% of cases, using MRS alone. The data obtained in the current study indicate that all four tumors could be distinguished based on combined differences in normalized metabolites and ADC values (Fig. 6). Although individual values may overlap, discriminant analysis using all seven variables was able to fully dissociate all four tumor patterns with a predictive score of 1 (certainty) in all cases. Nevertheless, several specific patterns must be first taken into consideration.

In agreement with previous studies \([32,39,41]\), all medulloblastomas in our study showed a consistent and significant elevation of Tau at 3.3 ppm (Fig. 8b, \( p < 0.001 \)) and a significant increase in Cho (Fig. 8c, \( p = 0.0021 \)). Tau is an aminosulfonic acid which localizes to the cerebellar molecular layer, Purkinje cells, basket cell axon terminals and glial processes, and is abundant in the developing cerebellum and isocortex. In vitro studies have demonstrated the presence in large concentrations of Tau in astroglial cells, which are enzymatically equipped for Tau synthesis and contain a high affinity transport system for this aminoacid \([1,23]\). Moreover, it has been speculated that increased Tau is associated with an increased cellular proliferation and tumoral aggressiveness \([14,24]\). As a matter of fact, bivariate analysis showed significant correlation between high
levels of Tau and Cho \( (p < 0.001, \text{Fig. 10}a) \). It has been previously demonstrated that high-grade tumors which are highly cellularized and have a high proliferative rate, show increased Cho levels in comparison to normal brain tissue [28,31]. In a pediatric population, high Cho levels seemed to correlate with tumor progression and a faster growth [34]. Experimental evidence suggests that accelerated anabolic pathways as well as oncogenic- or mitogenic-induced catabolic pathways of the major membrane phospholipids phosphatidylcholine and phosphatidylethanolamine induce an accumulation of phosphocholine and phospho-ethanolamine in actively proliferating cells [3,12,26,29]. This results in an enhancement of the so-called “tCho-peak” in malignant brain tumors. Hence, increase in Cho probably reflects two metabolic pathways in malignant tissues: an accelerated phosphorylation of Cho and ethanolamine or synthesis of membrane phospholipid precursors on one side [13,16], and a cleavage of phosphatidylcholine and phosphatidylethanolamine into phosphocholine and phosphoethanolamine on the other [7,19,20]. When considering the DWI characteristics of posterior fossa tumors, our results are consistent with literature data [13] with ADC values being significantly lower in medulloblastoma than in all other tumors (\( \text{Fig. 8a, } p < 0.001 \)). Bivariate analysis showed a significant negative correlation between ADC values and Tau and Cho (\( \text{Fig. 10b,d} \)). These findings underline the possible importance of ADC, Tau and Cho together, as biomarkers of higher malignancy in medulloblastomas.

Differentiation between ependymoma, pilocytic astrocytoma and infiltrating glioma is not as straightforward. Pilocytic astrocytoma is considered the most benign of all four histologic types. In our study, ependymoma and infiltrating glioma show higher levels of mI compared to medulloblastoma and pilocytic astrocytoma (\( \text{Fig. 9, } p = 0.023 \)). It has been suggested that mI level could be used as a marker for tumor grading in astrocytoma, while higher levels could be found in low grade astrocytoma compared to higher grade astrocytoma or glioblastoma [6,9]. The fact that the concentration of pooled mI was lowest in the most aggressive and malignant tumors, is not surprising. The portion of this mI that is visible by proton MRS is converted into phosphatidylinositol, which is a membrane phospholipid and is not visible on MR spectra [21,36]. The size of our cohort is nevertheless not large enough to permit any conclusion on that precise point.

When considering all parameters together, several factors may contribute to the better statistical discrimination between tumor groups when compared to other methods. First, the use of two groups of variables originating from different techniques provides two original points of view and separate insights into the physico-chemical properties of the tumors. It has been shown before, that in adult patients with gliomas, which demonstrate a positive correlation between tumor cellularity and ADC [10] as well as a
negative correlation between Cho ad ADC [5], the combination of DWI and MRS allows a more accurate interpretation with respect to tumor proliferative potential. Those previous results provide support for our current findings in this pediatric population. Second, the use of a more reliable reference and internal standard such as water signal (especially compared to Cr or Cho) for normalization of the metabolites, is a key step to eliminate inherent inconsistencies related to metabolite ratios. Indeed, when normalizing metabolites to Cr, the probability of correctly identifying tumors in our series sharply decreases (Fig. 7). Third, the use of short echo time MRS, still a more demanding technique in terms of analysis than long echo time spectroscopy, allows the detection of metabolites which have been suggested useful in the diagnosis of specific tumor histology.

In conclusion, linear discriminant analysis using short echo time single-voxel 1H-MRS combined with DWI fully discriminates the four most frequent posterior fossa tumors in children. This not only provides a better pathophysiological understanding, but will help clinicians in their therapeutic choices, especially in cases of inoperable tumors.

References


