A Diagnostic Algorithm for Posterior Fossa Tumors in Children: A Validation Stud

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Abstract

Background and Purpose

This study aimed to validate the clinical usefulness of a radiological decision flowchart based on previous published neuroradiological knowledge for the diagnosis of posterior fossa tumors in children.

Material and Methods

A retrospective study was conducted (January 2013-2019) at two pediatric referral centers, Hospital 1 and Hospital 2. Inclusion criteria were: age under 18-years-old, and histologically and molecularly confirmed posterior fossa tumors. Subjects with no available preoperative MRI study, and with tumors located primarily in the brainstem were excluded. Imaging characteristics of the tumors were evaluated following a pre-designed, step-by-step flowchart. Agreement between readers was tested with Cohen's Kappa, and each diagnosis was analyzed for accuracy.

Results

A total of 148 cases were included, with a median age of 3.4 years (IQR 2.1-6.1), and a male to female ratio of 1.24. The pre-designed flowchart facilitated identification of pilocytic astrocytoma, ependymoma, and medulloblastoma *sonic hedgehog* tumors with high sensitivity and specificity. Based on the results, the flowchart was adjusted so that it would also be able to better discriminate atypical teratoid/rhabdoid tumors and medulloblastomas groups 3 or 4 (sensitivity 75-79%; specificity 92-99%). Moreover, our adjusted flowchart was useful in ruling out ependymoma, pilocytic astrocytoma, and medulloblastomas *sonic hedgehog*.

Conclusion

The modified flowchart offers a structured tool to aid in the adjunct diagnosis of pediatric

posterior fossa tumors. Our results also establish a useful starting point for prospective clinical studies and for the development of automated algorithms, which may provide precise and adequate diagnostic tools for these tumors in clinical practice.

Abbreviations: AT/RT: atypical teratoid/rhabdoid tumor; PA: Pilocytic astrocytoma; WHO: World Health Organization; *NOS*: not otherwise specified; *SHH*: sonic hedgehog; *WNT*: wingless

Introduction

In the last 10 years, there has been an exponential increase in knowledge of the molecular characteristics of pediatric brain tumors, which was only partially incorporated in the 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System(1). The main update in the 2016 Classification was the introduction of the molecular profile of a tumor as an important factor for predicting different biological behaviors of entities which, on histology, look very similar or even indistinguishable(2). A typical example is the four main groups of medulloblastoma: wingless (*WNT*), sonic hedgehog (*SHH*) with or without p53 mutation, group 3, and group 4. Though they may appear similar on microscopy, these categories have distinct molecular profiles, epidemiology, prognosis, and embryological origin(3).

Subsequent to the publication of the 2016 WHO Classification, further studies have identified even more molecular subgroups of medulloblastoma with possible prognostic implications(4), and also at least 3 new molecular subgroups of atypical teratoid/rhabdoid tumor (AT/RT)(5), and several subgroups of ependymoma(6). MRI shows promise as a modality for differentiating histological tumors and their molecular subgroups. This capability relies not only on various imaging characteristics, but also on location and spatial extension of the tumor, evident on MRI, which can be traced to the embryological origin of the neoplastic cells(5,7,8,9,10).

One approach to the challenge of identifying imaging characteristics of different tumors in children is to use artificial intelligence. Yet despite this exciting innovation, correctly identifying the location of the mass and its possible use as an element for differential diagnosis still requires the expertise of an experienced radiologist. Previously, D'Arco et al proposed a flowchart [Figure 1] for the differential diagnosis of posterior fossa tumors in children based on epidemiological, imaging signal, and location characteristics of the neoplasm(12). The aims

of the current study are to: 1) validate the diagnostic accuracy of that flowchart in a retrospective large cohort of posterior fossa tumors from two separate pediatric tertiary centers based on previous neuroradiological knowledge for the diagnosis of posterior fossa tumors in children, 2) to describe particular types of posterior fossa lesions that are not correctly diagnosed by the initial flowchart, and 3) to provide an improved, clinical accessible flowchart based on the results.

Material and Methods

Setting and Subjects

A retrospective, cross-sectional study from two large tertiary referral pediatric hospitals in two countries (Hospital 1 and Hospital 2) was performed based on patient records spanning from January 2013 to October 2019, in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement(13). This study was conducted under two research protocols (BLINDED FOR PEER REVIEW), approved by the respective Institutional Review Board at each center.

Subjects were identified by electronic search of brain MRI reports and the electronic health record systems. The following terms/diagnoses were used for the search: “brain tumor,” “posterior fossa tumor,” “brain neoplasia,” “posterior fossa neoplasia,” “cerebellar tumor,” “cerebellar neoplasia,” “medulloblastoma,” “AT/RT,” “atypical teratoid/rhabdoid tumor,” “ependymoma,” “pilocytic astrocytoma.” Results were screened and subjects under 18 years of age with histologically and also genetically confirmed diagnosis of posterior fossa tumor, according to the 2016 WHO classification, were selected (2). Subjects with no available preoperative MRI study, those with low-quality MRI studies, and those without diffusion imaging on their MRI study were excluded. Subjects with tumors located primarily in the brainstem were also excluded.

Variables

Age at first MRI (before histological/pathological confirmation of the tumor), sex, and histologic and genetic/molecular results were obtained from electronic medical records. Two experienced pediatric neuroradiologists independently reviewed these initial MRI studies at each institution (BLINDED FOR PEER REVIEW), blinded to the final diagnosis. Imaging characteristics were evaluated following a step-by-step numerical flowchart, with a digit

assigned to each level and subsequent branch, providing a flowchart three-digit numerical sequence code for each diagnosis endpoint to be used in the analysis (Figure 1). The flowchart took into account: A) tumor location, B) ADC map signal intensity in comparison to grey matter, C) internal architecture, D) contrast enhancement, and E) patient's age. The flowchart was designed prior to the initiation of the study; it was based on a review on the topic by D'Arco et al (12). Prior to starting the blind analysis of the cohort, one of the readers (BLINDED FOR PEER REVIEW) performed a pilot evaluation using the first 8 cases from each institution (16/148; 10,8%) in order to confirm the applicability of the flowchart, multiple weeks before the formal evaluation.

Statistical analysis

Visual inspection of the histogram showed non-normal distribution, which was confirmed with the Shapiro-Wilk test ($p < 0.001$) for all numerical variables. Categorical variables are described with percentage and frequency, while numerical variables with median and interquartile range (IQR). Statistical analysis was performed using the R statistical software version 3.5.3 for windows.

Diagnotic accuracy of the flowchart was verified through a 2x2 contingency table and calculation of sensitivity (Se), specificity (Sp), positive predictive values (PPV), and negative predictive value (NPV). In order to estimate accuracy and effect size, CI of 95% was estimated for Se, Sp, PPV, and NPV. The diagnostic accuracy analysis was done for each diagnosis, with molecular/histologic diagnosis as the gold standard comparison. Since flowchart numerical sequences *312* and *311* of the pre-designed flowchart would not provide a single unique final tumor molecular diagnosis, we later adjusted the sequences according to the most prevalent diagnosis. The modified flowchart reflects these adjustments. Lastly, we recalculated diagnostic accuracy tests based on the adjustments done for these two flowchart modifications. The clinical applicability of findings was further explored with positive and negative likelihood ratios (LR+ and LR-, respectively), and based on changes in probability from LR described by McGee(14). Clinical applicability to rule-in diagnosis was considered if 95% CI of LR+ was above 10. Clinical applicability to rule-out diagnosis was considered if 95% CI of LR- was below 0.5.

Results

Histological diagnosis and demographics

One hundred and forty-eight (148) subjects were included. Median age at MRI was 3.4 years, interquartle range, IQR= 2.1 - 6.1 years), and the male-to-female ratio was 1.24. Fifty-four (36.5%) patients had a histological diagnosis of medulloblastoma, 56 (37.5%) had pilocytic astrocytoma (PA), 12 (8.1%) had atypical teratoid/rhabdoid tumor (AT/RT), and 19 (12.8%) had ependymoma. Medulloblastomas were also subclassified according to molecular subtypes including 14/54 (26%) *SHH*; 7/54 (13%) *WNT*; 5/54 (9%) Group 3; 9/54 (17%) Group 4; and 19/54 (35%) Group 3 or 4 (separation of group 3 and 4 not always easily possible). Seven cases (5%) had a diagnosis of other tumors not covered by the flowchart (2 low-grade diffuse astrocytomas not otherwise specified (*NOS*), 1 hemangioblastoma, 2 gangliogliomas, 1 Langerhans cell histiocytosis, and 1 meningioma). Agreement between readers at each institution was very high ($\kappa = 0.96$ for both institutions, $p < 0.001$). As both institutions had almost perfect agreement, we did a pooled analysis without differentiating per institution. The same diagnosis using the pre-designed flowchart was reached for 86% of the cohort. In the 14% of cases in which the same diagnosis was not reached by the two readers, disagreement was solved through consensus between the readers.

Diagnosis using the flowchart

Using the pre-designed flowchart (Figure 1), the most common diagnosis was PA (numeric sequence *123*) (n=53, 36%), followed by medulloblastoma all subgroups (numeric sequence *312*) (n=35, 24%), ependymoma (numeric sequence *323*) (n=17, 11%), medulloblastoma *SHH* (numeric sequence *111*) (n = 10, 7%), medulloblastoma group 4 or AT/RT (numeric sequence *311*) (n = 5, 3%), AT/RT (numeric sequence *411*) (n = 7, 5%), ependymoma (numeric sequence *423*) (n = 7, 5%), desmoplastic medulloblastoma *SHH* (numeric sequence *112*) (n = 6, 4%), desmoplastic medulloblastoma *SHH* (numeric sequence *313*) (n = 3, 2%), and medulloblastoma *WNT* (numeric sequence *412*) (n = 5, 3%). Figure 2 and Table 1 show the statistical results of Se, Sp, PPV and NPV of the flowchart per diagnosis.

In cases that followed sequence *311* (medulloblastoma group 4 or AT/RT), 3/5 (60%) were AT/RT, 1/5 (20%) was an ependymoma, and 1/5 (20%) was a medulloblastoma group 4. This suggested that sequence *311* catches more tumors in the AT/RT category than in medulloblastomas group 4, so we re-calculated diagnostic accuracy tests considering both *311* and *411* as AT/RT. As can be appreciated in Figure 2 and Table 1, diagnostic accuracy for AT/RT cases improved when combining sequences *311* and *411*. Of the 35 cases under sequence *312* (medulloblastoma all subgroups), 26/35 (74%) were confirmed as group 3 or 4

(3 confirmed group 3; 8 confirmed group 4; and 15 group 3 or group 4). The remaining cases under sequence *312* were: 3/35 (9%) *SHH*, 5/35 (14%) *WNT*, and 1/35 (3%) AT/RT. Figure 3 shows the diagnostic accuracy of sequence *312* to identify medulloblastoma *SHH*, *WNT*, and group 3 or group 4. For this sequence, the NPV and Sp were higher than the PPV and Se for all other sequences. Table 2 shows LR analysis per diagnosis and the recommended sequences for the diagnosis. After our analysis, and based on Table 1 results, we modified the pre-designed flowchart with more precise categorization of types of tumor. We recommend this new flowchart (Figure 4) for diagnosis of posterior fossa tumors in children.

Some examples of differentiating posterior fossa tumors from our cohort, diagnosed based on the new flowchart here presented, can be seen in Figures 5 and 6.

Discussion

The 2016 introduction of the new classification of brain tumors based on histological and molecular characteristics dramatically changed the management of pediatric brain tumors (1,2,15,16). The fact that tumors with similar histological appearances can be related to completely different cellular populations, with different molecular profiles and different embryological origins, implies that they develop along different cellular paths. Thus, tumors that were previously considered as a single group can now be differentiated on imaging by location, age, and/or the patient's signal characteristics, resulting in a more accurate prognosis (17,18,19).

In light of the crucial role of molecular profiling in tumor diagnosis and management, we found that the pre-designed flowchart was very useful for categorizing and better understanding pediatric brain tumors. The importance of molecular profiling in the pediatric neuro-oncology clinical practice was first studied in medulloblastomas, but is now recognised for ependymomas, low-grade astrocytomas, AT/RT, and all previously classified primitive neuroectodermal tumors (PNET)(6,19–23).

Yet, since the 2016 classification update, several newly identified radiological markers have been proposed as surrogates for the molecular diagnosis. The role of these radiological markers may be limited by the constant evolution of the molecular characterization of brain tumors (8,12). However, we believe a standardized method of evaluating images, such as the proposed flowchart, may facilitate increased diagnostic accuracy.

The initial diagnostic flowchart was proven reliable and consistently accurate in this validation study, with an almost perfect agreement between two blinded neuroradiologists at two different institutions. Our results showed high coefficients of specificity and NPV for all diagnoses included in the pre-designed flowchart. Sensitivity coefficients were high (> 87%) for diagnosing pilocytic astrocytoma and ependymomas, the two most common diagnoses in our cohort. Moreover, PA and ependymoma tumors had the smallest CI at 95%, suggesting reliability in the diagnosis of these two types of tumors. This was especially true for PA, in which the lower CI limit for sensitivity was 76% and for PPV was 82%.

After analyzing results from the initial flowchart created based on literature, we modified it to improve diagnostic accuracy. Our modifications (see Figures 1 and 4 for comparison) successfully improved the sensitivity coefficient for identification of AT/RT to 75%, but the CI remained wide. The second modification, to the flowchart sequence *312*, was able to identify most cases of medulloblastomas group 3 or 4, with fair to good sensitivity (61-91%) and PPV (57-88%), and good to excellent specificity (86-96%) and NPV (88-97%). The modified flowchart (Figure 4) proved to be more clinically relevant. The modified flowchart proved quite capable of discriminating AT/RT, ependymomas, medulloblastomas *SHH*, medulloblastomas group 3/4, and PA, which together constitute 90.5% of tumors in our cohort. Clinically, the flowchart demonstrates great performance in ruling out group 3 or 4 medulloblastomas, PA, and ependymomas, and to rule in AT/RT tumors.

However, when it came to correctly identifying *WNT* medulloblastoma (numeric sequence 412, Figure 2), diagnostic accuracy was poor. In the pre-designed flowchart, the authors designated a tumor in the ponto-cerebellar angle/foramen of Luschka with high cellularity (i.e., low ADC) and patient age above 3 years as suggestive of *WNT*. The rationale was that the cellular path of embryological precursors, which can transform in neoplastic *WNT* cells, arises from the fourth ventricle down and laterally into the foramen of Luschka(7). The only other tumor with striking diffusion restriction in the Luschka area is AT/RT, but this is typical of younger children(24). However, these results can be explained by several factors: the small number of *WNT* present in our series (10% of all medulloblastomas)(25), the fact that most of the cases in our series were in the fourth ventricle (which is understandable given that the path of the *WNT* cells is thought to start from the fourth ventricle), and the presence of anaplastic ependymomas showing diffusion restriction (therefore simulating *WNT* medulloblastoma on imaging). More

recently, a study of a larger cohort of WNT medulloblastoma has shown that they are not as lateralizng as previously reported in smaller cohorts(26).

This study has some limitations, the main one being its retrospective nature. However, we controlled potential biases by doing a blinded review of images, by only including cases with images taken prior to surgical intervention, and by creating the baseline flowchart prior to data collection. Another important limitation is the relative small number of cases for some types of tumor which explains the larger confidence intervals for certain tumors. Nevertheless, many pediatric cerebellar tumors are relatively rare, and this is perhaps one of the largest cohorts available in the literature(27). Moreover, we were able to gather a large enough cohort to allow for diagnostic accuracy tests for the most common types of pediatric cerebellar tumors, with reliable results for most diagnoses. Since this was planned as a validation study, we consider it successful in providing results that show the modified flowchart can be used, is reliable, and has clinical applicability. More research is still desired, with a larger consistency analysis evaluating results from multiple blinded readers. A larger prospective study would be needed to evaluate the diagnostic efficacy of the modified flowchart with higher precision. Such a study could provide an initial decision model for potential deep learning studies. Artificial intelligence is already being used to predict the molecular profile of brain tumors, most commonly in adult populations, but with recent important studies emerging in pediatric populations(11,28).The main limitation for the application of machine learning in posterior fossa tumors may be the identification of tumor location(29), since we know that signal characteristics (which reflect at least partially histological appearances) can be similar for different molecular groups with similar tissue features. Currently, artificial intelligence is not able to differentiate tumors with the necessary level of precision, though this may be possible in the future.

Conclusion

A flowchart for the diagnosis of posterior fossa tumors in children has been validated through a retrospective analysis of 148 patients with confirmed diagnoses. Based on analysis of these results, the pre-designed flowchart was accurate in identifying most diagnoses, and with our subsequent modifications, the overall accuracy improved. The modified flowchart showed a good likelihood ratio for most of the histologic and molecular groups of tumors. Furthermore, it may offer an important starting point for prospective analysis using machine learning techniques. As new molecular subgroups emerge in the classificaiton of pediatric brain tumors,

there is potential for further modifications to the flowchart to aid in diagnosis.

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Tables and figures

Table 1. Statistic analysis of the radiologic flowchart to discriminate different types of cerebellar tumors.

Diagnosis equivalent	Flowchart Sequence	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Ependymoma	*323 / 423*	89 (67-99)	95(89-98)	71 (49-87)	98 (94-100)	94 (89-97)
Pilocytic astrocytoma	*123*	88 (76-95)	96 (89-99)	92 (82-98)	93 (85-97)	93 (87-96)
AT/RT	*411*	50 (21-79)	99 (96-100)	86 (42-100)	96 (91-98)	99 (96-100)
AT/RT	*411 / 311*	75 (43-95)	98 (94-100)	75 (43-95)	98 (94-100)	91 (96-98)
Medulloblastoma *SHH*	*111 / 112 / 313*	71 (42-92)	93 (88-97)	53 (29-76)	97 (92-99)	72 (64-79)
Medulloblastoma *WNT*	*412*	14 (0-58)	97 (93-99)	20 (1-72)	96 (91-98)	88 (93-97)

Table 2. Likelihood ratio analysis of the radiologic flowchart to discriminate different types of cerebellar tumors.

Diagnosis	Flowchart Sequence	LR+ (95% CI)	LR- (95% CI)
AT/RT	*411/311*	34 (10.6-109)*	0.26 (0.1-0.7)
Ependymoma	*323/423*	16.5 (7.9-35)	0.11 (0.03-0.4)*
Medulloblastoma *SHH*	*111/112/313*	10.6 (5.2-21.7)	0.3 (0.1-0.7)
Medulloblastoma group 3 or 4	*312*	10.07 (5.3-19.3)	0.23 (0.12-0.45)*
Pilocytic astrocytoma	*123*	20 (7.7-52.8)	0.13 (0.13-0.26)*

*Clinically applicable confidence intervals (CI)

Figure 1. Pre-designed radiologic flowchart created according to the literature before diagnostic accuracy analysis. *Brainstem tumors excluded from the analysis. ** Relative to grey matter.

Figure 2. Diagnostic accuracy of a pre-designed radiologic flowchart to identify different types of cerebellar tumors.

Figure 3. Diagnostic accuracy of sequence *312* (all types of medulloblastomas) of the pre-designed radiologic flowchart to identify different types of medulloblastomas.

Figure 4. Modified radiologic flowchart (Flowchart 2) after diagnostic accuracy analysis. *Brainstem tumors excluded from the analysis. ** Relative to grey matter.

Figure 5. Differential diagnoses in cases of posterior fossa tumors originating from the cerebellar hemisphere. Axial T2 WI (A) and axial ADC map (B) show *SHH* medulloblastoma (Flowchart 2 number *111)* in typical peripheral location within the cerebellar hemisphere due

to its origin from ganglionic cell precursors. Note very low ADC values (i.e., diffusion restriction). Axial T2 WI (C) and axial ADC map (D) show typical appearance of a pilocytic astrocytoma (Flowchart 2 number *123*) originating from the cerebellar hemisphere. Note the typical nodule and appearance of cysts and much higher ADC values in comparison with the medulloblastoma.

Figure 6. Differential diagnoses in posterior fossa tumors involving the foramen of Luschka and cerebellopontine angle. Axial T2 WI (A) and ADC map (B) in a child with ependymoma (Flowchart 2 number *423*). Note the presence of internal vessels (arrow) and intermediate ADC values. Axial T2 (C) and ADC maps (D) in a 2 year-old boy with AT/RT (new flowchart number *411).* Note very low values of ADC, suggesting an embryonal tumor and peripheral cysts.