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## **Posterior fossa tumors in children: Radiological tips & tricks in the age of genomic tumor classification and advance MR technology.**

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# **Posterior fossa tumors in children: Radiological tips & tricks in the age of genomic tumor classification and advance MR technology.**

## **Abstract**

Imaging plays a major role in the comprehensive assessment of posterior fossa tumor in children (PFTC). The objective is to propose a global method relying on the combined analysis of radiological, clinical and epidemiological criteria, (taking into account the child's age and the topography of the lesion) in order to improve our histological approach in imaging, helping the management and approach for surgeons in providing information to the patients' parents. Infratentorial tumors are the most frequent in children, representing mainly medulloblastoma, pilocytic astrocytoma and brainstem glioma. Pre-surgical identification of the tumor type and its aggressiveness could be improved by the combined analysis of key imaging features with epidemiologic data.

## **Keywords**

Brain; Pediatric; Magnetic resonance imaging; Posterior fossa; Tumor

## **Introduction**

We know how imaging is crucial in the comprehensive assessment of posterior fossa tumor in children (PFTC). First of all, in the presence of suggestive clinical symptomatology, it provides the diagnostic and identifies acute complications which could require emergency care. Secondly, imaging remains the gold standard to evaluate central nervous system distant extension. Imaging is also a key in the histological approach of these tumors.

This histological approach has been revolutionized recently by the advent of genomic technologies on the one hand [1–4] and through the development of advance MR techniques on

the other. Nevertheless, it remains challenging in radiology to approach the histology of PFTC because none of the imaging features are specific [3].

The objective of this pictorial review is to propose a global method relying on the combined analysis of radiological, clinical and also epidemiological criteria, (taking into account the child's age and the topography of the lesion) in order to improve our histological approach in imaging, helping the management and approach for surgeons in providing information to the patients' parents.

Although this article is not intended to be an exhaustive review of posterior fossa tumors (already done by recent very complete articles[3–7]), the key points of the characteristics of each tumor will be exposed in the second part.

## **Body text**

### *Keys features for pre-surgical identification of the tumor type and its aggressiveness*

#### *1.1. Epidemiologic consideration*

Central nervous system tumors are the most common cancers among those aged 0-19 years, with an average annual age-adjusted incidence rate of 5.57 per 100,000 population and represent the second cause of death from cancer in childhood [8,9]. Infratentorial tumors account for 45-60 % of all pediatric brain tumors [10]. Most of posterior brain tumors are discovered between 3 and 11 years old [8,9]. Overall, Medulloblastoma represent 30-40%, pilocytic astrocytoma 25-35%, brainstem glioma 20-25%, ependymoma (EP) 10-15%, atypical teratoid rhabdoid tumor (ATRT) less than 1-2% and other histological types 10-15% of posterior brain tumors [5]. Nevertheless, the prevalence of the different types of tumor is in fact deeply influenced by their location. For example, high grade glioma (HGG) is by far the most common tumor in the pontine [3,5], whereas medulloblastoma and pilocytic astrocytoma are the

first tumors in the cerebellum] [3,5]. On the basis of our experience, we suggest (for information purpose only) a prevalence rearrangement taking into account the topography in Figure 1.

Age is also an important clinical data to consider. For example, ATRT accounts overall for less than 1-2% of pediatric brain tumors, however according to some authors, this rate could rise to 6-7% if we only considered children younger than 2 [10,11].

### *Radiological tips & tricks*

#### *Topographical clues*

Faced with a brainstem tumor, the pontine involvement is the key element to look for, because it is highly evocative of high grade glioma H3 K27M-mutant (58/66 in the Raybaud and all pontine brainstem tumor series) [3]. Pontine involvement is defined by a tumor that partially or totally infiltrates the pons (and not only those centered on the pons). The anterior or antero-lateral exophytic extent in the pre-pontine cistern is typical of HGG. Those tumors often surround the basilar artery without thrombosis. [3,5,12]. Conversely, a brainstem tumor which spares the pons is very likely to be a low grade glioma (LGG) (44/48 in the Raybaud and all extra-pontine brainstem tumor series) [3]. Preferential locations of LGG are the tegmentum, the brachium pontis and the lateral part of the medulla[3] (fig 2).

For the tumors of the fourth ventricle, the best clue is the ability of the lesion to adapt its shape to its container and to escape through the lateral apertures of Luschka or median aperture of Magendie to the great cistern. Even if this feature is nonspecific it would suggest an ependymoma [3,5]. Conversely the medulloblastoma (mainly

wingless integration (WNT) and Group 4 subtypes) which is the first tumor type of the fourth ventricle, would more likely stay in the ventricle and extend its container[3–5] (fig 3).

For the assessment of cerebellum tumors, instead of the anatomic distinction of vermian and hemispherical tumors, it could be more relevant from a radiological point of view, to consider separately the postero-lateral tumors on one side and the anterior tumors on the other (Fig 1). In the postero-lateral cerebellum the first tumor type is pilocytic astrocytoma followed by medulloblastoma (mainly sonic hedgehog (SHH) subtype or type 3)[3,4,10]. Another rare and very aggressive embryonal tumor like ATRT should be considered before 3 years of age [10,11]. ATRT would more likely extend to the cerebello-pontine angle [5,11]. Much less frequently, bone or meningeal aggressive tumors should be evoked, in which the extra-parenchymal location could be challenging to assert, mostly in case of parenchymal infiltration [13]. The anterior part of the cerebellum can be viewed as a transitional area where we can find both cerebellum lesions, such as pilocytic astrocytoma and also tumors arising from the anterior anatomic structures, like 4<sup>th</sup> ventricle's medulloblastoma (mainly WNT subtype) or glioma of the brachium pontis [3].

In the cerebellum pontine angle, extra parenchymal lesions such as schwannoma and meningioma are rare in pediatric and occur almost entirely in NF2 genetic syndrome [13]. Most of the time, tumors that develop in this area come from the adjacent brain structures and a high aggressiveness rate is reported [14].

Finally, diffuse leptomeningeal glioneuronal tumor is a rare new entity in the 2016 World Health Organization (WHO) Central Nervous System tumour classification. Three phases have been described in imaging. Most of the time, brain and spinal cord

leptomeningeal nodular enhancement is the first aspect of this tumor type. The second phase is characterized by the presence of multiple leptomeningeal cysts. Then, a dominant lesion becomes individualizable [6,15].

### *Structural imaging*

The solid or micro-cystic tumor's morphology is not discriminant [3]. Nevertheless a cystic lesion with an eccentric solid component or a thick border would suggest a pilocytic astrocytoma [5]. Haemorrhage is not discriminant [3,5]. Calcifications are nonspecific of any lesion but are most frequently found in ependymoma (around 50% of cases) [16]. Spontaneous high CT scan density or low T2 signal (and also high diffusion with low ADC) is evocative of embryonal pediatric's posterior fossa tumors (medulloblastoma or ATRT) [5,16].

Regarding the enhancement pattern, only a weak or absent enhancement is evocative of LGG in the pons or groupe 4 medulloblastoma of 4<sup>th</sup> ventricle [3–5]. Other enhancement patterns are indiscriminant [3].

### *Advance MR technologies*

#### *Diffusion sequence*

Several studies have shown that diffusion characteristics of the common pediatric cerebellar tumors may be helpful in rendering an accurate preoperative diagnosis [17–23]. The majority assessed the accuracy of direct tumor ADC values (mean ADC or minimal ADC values) and/or the tumor/normal ADC ratio.

Mean ADC values is the most studied and in turn probably the most robust parameter [17–20]. The optimal threshold to discriminate the tumors seems to be very consistent across studies (Supplemental table 1). For the current practice, we could use the results

of the study by Koral *et al.* [20], which is the largest sample size study with 140 pediatric posterior fossa tumors. In this study, ADC ratio of  $\geq 1.8$  correctly discriminated pilocytic astrocytomas from ependymomas with a sensitivity of 0.83 and a specificity of 0.78. ADC ratio of  $<1.2$  correctly discriminated ependymomas from embryonal tumors with a sensitivity of 0.87 and a specificity of 0.83. In this same reference study, mean ADC values has shown good accuracy as well: mean ADC values of  $\geq 1.4 \times 10^{-3} \text{ mm}^2/\text{s}$  correctly discriminated pilocytic astrocytomas from ependymomas with a sensitivity of 0.75 and a specificity of 0.86 and mean ADC values of  $<0.85 \times 10^{-3} \text{ mm}^2/\text{s}$  correctly discriminated ependymomas from embryonal tumors with a sensitivity of 0.82 and a specificity of 0.67 (see table 1).

Concerning minimal ADC values, overlap has been reported between medulloblastoma and ependymoma in the study of Jaremko et al [21].

It is interesting to note, regarding the radiological/anatomopathology confrontation, that despite the fact that the vast majority of authors associate ADC value and tumor cellularity, Koral et al have shown that the cellularity may not be the sole determinant of the differences in diffusivity of child posterior fossa tumors [24].

Concerning diffuse intrinsic pontine glioma, preliminary studies have examined the capability of diffusion to reflect the aggressiveness of those tumors but further investigations are required [25].

In the future, ADC histogram as well as metrics and textural features of MRI diffusion could be some interesting tools for differentiation of PFTC and even maybe for medulloblastoma subtypes [26,27].

*Magnetic Resonance Spectroscopy:*

An increase of choline is not very discriminating because it may be seen in most of the different fossa posterior tumors including PA, which is a typical low grade neoplasm. Note however that the distinction between an atypical laminated medulloblastoma and a Lhermitte-Duclos disease could be challenging. In this special situation a high peak of Choline in favour of medulloblastoma could be very helpful. A peak of Taurine at 3.35 ppm is very evocative of medulloblastoma. A peak of myo-inositol at 3.5 ppm is evocative of ependymoma (but it can sometimes also be seen in desmoplastic medulloblastoma). Finally, a decrease of Creatinine at 3.03 ppm is evocative of pilocytic astrocytoma (see table 1) [5].

#### *Perfusion techniques:*

Classical T2\*-weighted Dynamic susceptibility contrast MRI (PWI) is challenging in pediatric imaging, mainly because it requires a large-bore intravenous access to ensure the high contrast flow required by the technique [28]. As a result, very few studies are available on this topic. However, PWI could be interesting for the differentiation of PA from Hemangioblastoma in older children, thanks to a significant difference between the  $rCBV_{max}$  of PA ( $rCBV_{max} = 1.19 \pm 0.71$ , range 0.6—3.27) compared with that of Hemangioblastoma ( $rCBV_{max} = 9.37 \pm 2.37$ , range 5.38—13) [29]. Ependymoma generally demonstrates elevated  $rCBV$  with a poor return to baseline and elevated K2 that should be attributed to fenestrated blood vessels and an incomplete brain blood barrier [16,30], however in our experience this PWI pattern could be found in other PFTC such as medulloblastoma.

T1-weighted Dynamic contrast enhanced MRI (DCE) have recently shown its feasibility in child brain oncology. Indeed, unlike PWI, only a low contrast flow (1-2

ml/s) is required by this technique which enables even small-bore intravenous access [27,31,32]. The first studies in children show that DCE could be of great value in differentiating brain tumor grades [27,31,32].

Arterial Spin Labeling (ASL) is certainly a promising technology in pediatric imaging with the interest of the absence of gadolinium injection[33]. Yeom and colleagues were the first to highlight the capability of tumor blood flow (TBF) measured by ASL to distinguish high-grade (III-IV) and low-grade (I-II) pediatric brain tumors. They also demonstrated that relative TBF was significantly higher for medulloblastoma compared with pilocytic astrocytoma among PFTC [28]. Kikuchi et al have shown a positive correlation between tumor blood flow (TBF) measured by ASL and histopathological vascular density in pediatric brain tumors. As a secondary end point, this study also suggests that TBF rate of high-grade (III-IV) tumors was significantly higher than that of low-grade (I-II) tumors [33].

#### *Multiparametric MR Combined algorithm*

Experimental studies assessed the accuracy predictive combined model bases on DWI PWI and MRS techniques with machine learning algorithms[27,34]. Vajepeyam et al have shown that ADC histogram metrics combined with permeability metrics differentiate low- and high-grade pediatric brain tumors with high accuracy[27]. In the study of Koob *et al*, the highest diagnostic accuracy for tumor grading was obtained with diffusion–perfusion (73.24 %) and for tumor typing with diffusion–perfusion–MR spectroscopy (55.76 %) [34].

#### *Central Nervous System distant localizations*

Initial multiple brain parenchyma localizations are evocative of hemangioblastoma or ATRT. Distant parenchymal recurrence has been described in the follow-up for HGG and embryonal tumors.

Meningeal and cisternal distant localizations are not rare in children's brain tumors and must be researched in the initial evaluation and during the follow up by cerebral and medullar MRI. All PFTC could be concerned but CSF metastases are most frequent with medulloblastoma (around 30% at the diagnosis).

### *1.1 General context*

Von Hippel Lindau disease is associated with hemangioblastoma. NF1 syndrome is associated with pontine glioma (mostly LGG) and NF2 syndrome with extra parenchymal schwannoma and meningioma. Gorlin, Turco and Li-Fraumeni syndromes are associated with a high rate of medulloblastoma.

*Key points of children's posterior fossa brain tumor:*

## 2.1 Embryonal pediatric's posterior fossa tumors: Medulloblastoma & ATRT

### Medulloblastomas

#### *Overview*

Medulloblastoma belongs to the group of embryonic neuronal tumors. These are the most common posterior fossa tumors (30-40%). They affect twice as many boys [2], with a double peak frequency: around 3 years and 9 years. It develops on the midline in 75 to 90% of cases, from the lower part of the vermis, and often invading the 4<sup>th</sup> ventricle roof. However, various locations including cerebellar hemisphere, are associated with special types of medulloblastoma (cf below). In imaging, medulloblastoma most often appears heterogeneous (necrosis, calcifications and cysts

are possible). Solid solitary mass is the most frequent presentation, but infiltrative patterns are possible. Spontaneous hyperdensity on CT and hypointensity on T2 (compared to gray matter) and of course on diffusion is evocative of medulloblastoma in PFTC. Tumor' ADC ratio lower than 1.2 and tumor's mean ADC values  $< 0.85 \times 10^{-3}$  mm/s is very evocative of embryonal tumors [20]. The enhancement is present most of the time (except in group-4 subtype: cf below). The spectroscopy is evocative if it shows a high Choline peak and above all a Taurine peak at 3.35ppm. medulloblastoma is the most often metastatic tumor at diagnosis. Lepto-meningeal metastases are observed in 1/3 of cases of medulloblastoma at diagnosis, but brain parenchymal, dural based, intraventricular metastasis are also classical.

### *Subtypes*

The recent advent of genomic technologies in brain oncology led to an update of the WHO classification in 2016. Indeed, for embryonic neuronal tumors in particular, previous studies have shown that taking into account the molecular profiling leads to a better correlation with imaging presentation but also with the prognosis of those tumors [1,2,35,36]. Genetics also allows new therapeutic approaches with the advent of targeted therapies. In this context, a precise topographical imaging assessment is more crucial than ever for a reliable pre-surgical identification of the tumor type and its aggressiveness[3].

Histological classification (Simplified in 3 groups): classical type, desmoplastic-nodular type and large anaplastic cells (LCA) type.

Molecular classification and related MRI appearance: Molecular tumor abnormalities can be directly associated with the anatomical origins of medulloblastoma [5]. This results in the following classification according to 4 groups [6]:

- WNT (wingless) : 11% of medulloblastoma, peak frequency between 10 and 12 years (almost never before 4 years old), very good long-term prognosis, mostly classical histology, must be suspected if centered on the lateral recess of the fourth ventricle or the brachium pontis (develop from the Wnt-expressing lower rhombic lip).
- SHH (Sonic hedgehog) : 28% of medulloblastoma, two peaks of frequency : <4years and >16years, intermediate prognosis (good in young children, poor in older subjects), mostly desmoplastic but any histological type possible, specific targeted therapies available, mostly located in the cerebellar hemisphere (develop from the shh-modulated cerebellar cortex).
- Group 3 (MYC amplification): 28% of medulloblastoma, rather young infants, worst prognosis, classical or LCA subtype, must be suspected when faced with a juxta-ventricular small principal tumor with an early local or distant meningeal dissemination.
- Group 4 (isochromosome 17q): 34% of medulloblastoma, Any age, intermediate prognosis, large V4 tumor complicated by hydrocephalus, slight or no enhancement is very evocative, dissemination is common.

## ATRT

It is a rare aggressive malignant tumor occurring before the age of 2-3 years. In this particular population, the prevalence is around 20%. It is characterised by the alterations of INI1 or, rarely, BRG1 genes [37]. The imaging aspect is very close to medulloblastoma. Cerebello-pontine angle invasion and multiple brain locations would be more frequent for this type of tumor than for medulloblastoma according to some authors.

### 3.1 Ependymoma

It is the fourth most frequent pediatric posterior fossa tumor. In the pediatric population the peak of frequency is before the age of 5. Complete surgical resection is the major prognostic factor. The vast majority (90%) is developed in contact with the 4<sup>th</sup> ventricle, however distant ependymal forms have been reported (it could be explained by some recent molecular works which have shown that ependymoma are derived from the radial glia cell). Imaging global aspect is heterogeneous. Several characteristics are in favour of this tumor (although none are pathognomonic): 1) The ability of the lesion to adapt its shape to its container and to escape through the lateral apertures of Luschka or median aperture of Magendie to the great cistern; 2) Intra-lesional calcifications (found in 50% in some series); 3) High myo-inositol peak at 3,5ppm; 4) ADC ratio between 1.2 and 1.8 [20]; 5) In perfusion the brain blood barrier leak (High K2 and poor return to baseline) seems to be evocative according to some authors [5].

### 4.1 Brainstem Glioma

Brainstem is the first location of glioma in the posterior fossa. As mentioned above, the pontine involvement is the key element to look for, because it is highly evocative of high grade glioma.

#### Pontine Glioma

Most of those tumors are high grade neoplasms or low grade at diagnosis but with an almost systematic and particularly rapid evolution towards higher grade. From a molecular point of view they are recently classified in the diffuse midline glioma, H3 K27M-mutant entity. Those diffuse midline tumors, extend the pons, compress and then

invade the other brainstem structures. They expand anteriorly in the pre-pontine cistern and often encircle the basilar trunk without invading it. They can deform the fourth ventricle, which is usually only partially collapsed without hydrocephalus upstream [3]. The imaging appearance is that found in most aggressive tumors without a characteristic pattern of this particular type. It includes, poorly defined contours, crossing of anatomic boundaries, pervasive oedema, heterogeneous signal related to necrotic or haemorrhagic contingents (globally highT2/FLAIR and lowT1). High diffusion non necrotic portions are not rare and have been related to a poorer survival [5]. The enhancement is very variable. In perfusion rCBV (neoangiogenesis) and K2 (brain blood barrier leak) are classically increased in the non-necrotic zones. A spectroscopy pattern is often typical of high-grade glial tumor with a massive Choline peak at 3.02 ppm (cellular turn over) and a decrease in NAA at 2.01 ppm (normal neuronal cells indicator).

#### Extra-pontine brainstem tumors

A brainstem tumor which spares the pons is very likely to be a low grade glioma (LGG) [3].

Most of them are H3 K27M-mutant glioma (but with a better prognosis than in the pons), pilocytic astrocytoma or ganglioglioma. The tegmentum, the brachium pontis and the lateral part of the medulla are the preferential locations. Those lesions are mostly homogeneous, well demarked and anatomic boundary crossing is unusual. Cystic remodelling is frequent, but necrotic or haemorrhagic components are rare. Diffusion restriction is unusual. The enhancement is variable and is not associated systematically with an aggressive tumor. Finally, the most important point is certainly the slow growth rate during the follow-up period.

### 5.1 Cerebellar pilocytic astrocytoma

This is the second most common posterior fossa tumor just after medulloblastoma (around 35% of the PFTC). About half develops from the vermis and the other half from the cerebellar hemispheres [5]. The mass effect is significant in most cases leading to a fourth ventricle collapse with hydrocephalus. The vast majority (around 2/3) of pilocytic astrocytoma are predominantly cystic with a solid wall nodule or a thick wall. The last third are predominantly solid forms. The low cell density of pilocytic astrocytoma's solid component is the key element to distinguish them from the other PFTC. This low density manifests itself on MRI by a hyper intensity on T2 images (compared to the cerebellar cortex), and above all it almost never shows restricted diffusion. ADC ratio higher than 1.8 and mean ADC values  $> 1,4 \times 10^{-3} \text{ mm}^2/\text{s}$  is very evocative of pilocytic astrocytoma [20]. Tumor bleeding is possible. Avid enhancement of the solid portion is the rule despite their low aggressiveness. Perfusion is classically used to differentiate pilocytic astrocytoma from hemangioblastoma; however this situation is actually very rare in pediatrics because hemangioblastoma is more of a young adult tumor. Choline is almost always very high in pilocytic astrocytoma and should not cause the diagnosis to be reconsidered.

### Conclusion

MRI is still a developing useful tool to analyze brain tumors in children. With some radiological tips and tricks, further information could be provided to surgeons and oncologists to improve care and information given to the parents and the child at the time of diagnosis.

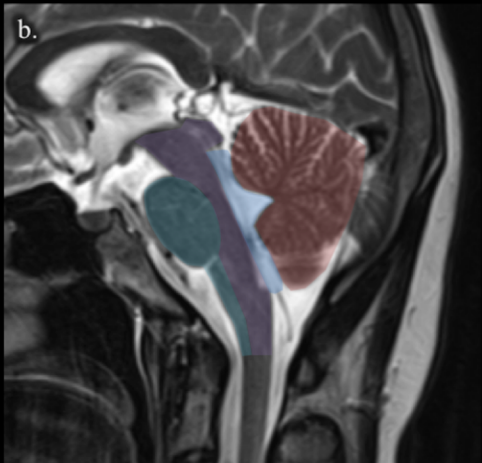
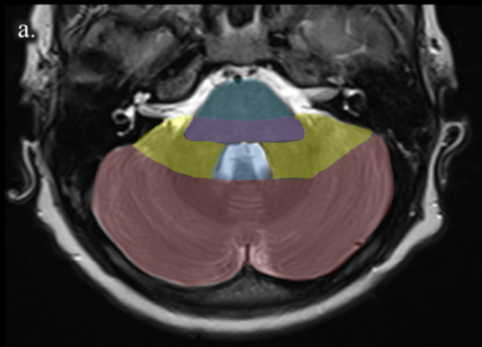
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◆ ***Pons :***

**HGG > LGG > GG**

◆ ***Brainstem out of the pons***

**LGG > GG**

◆ ***Fourth ventricle***

**MB > EP**

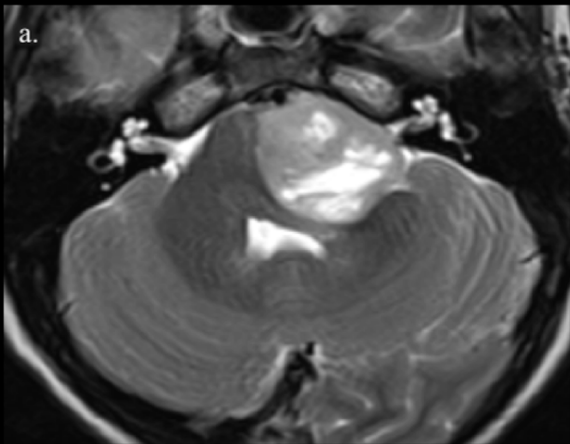
◆ ***Anterior cerebellum***

**LGG / MB / PA**

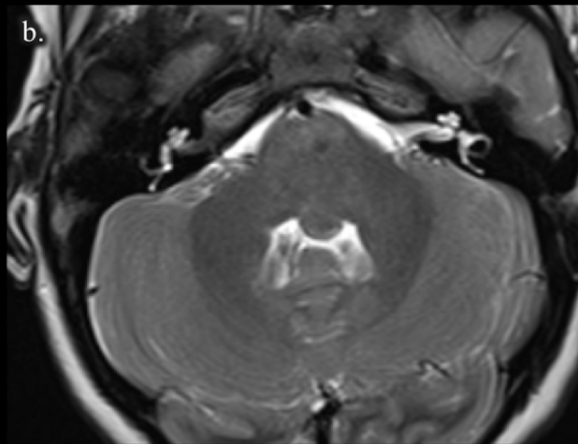
◆ ***Posterior cerebellum***

**PA / MB**

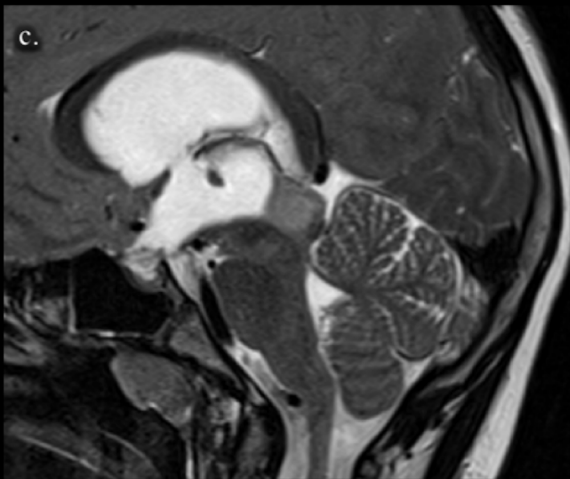
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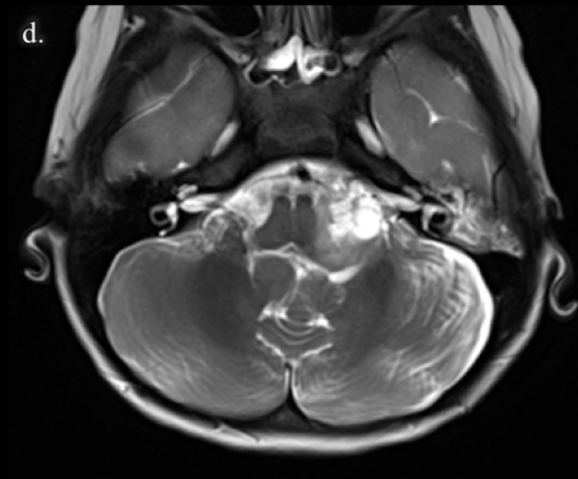
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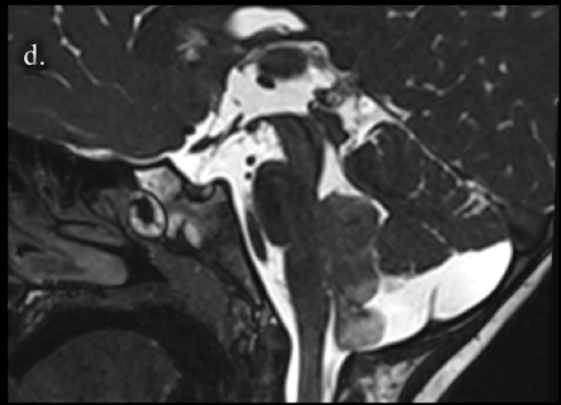
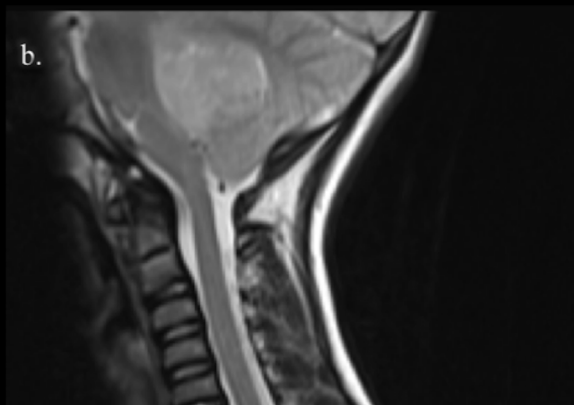
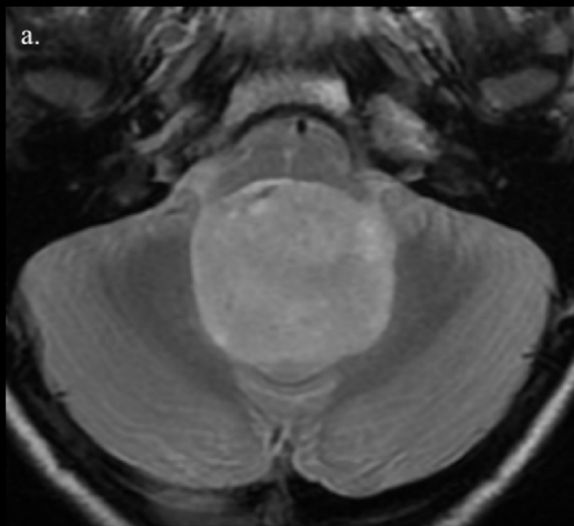


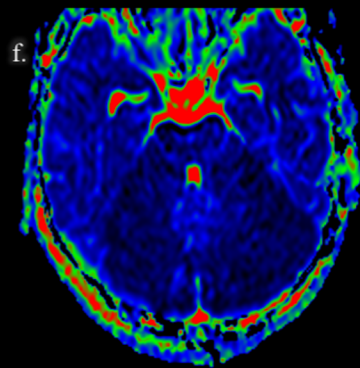
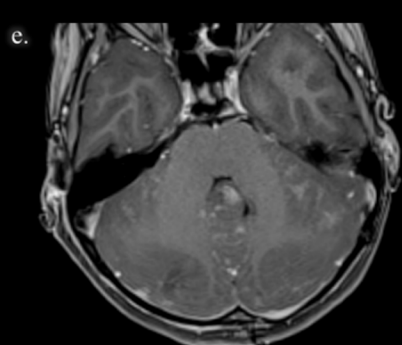
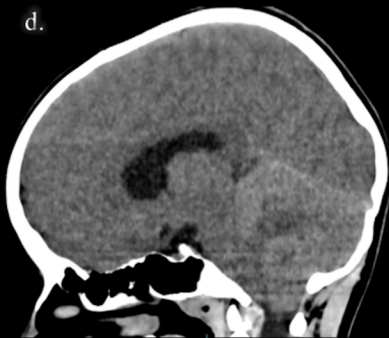
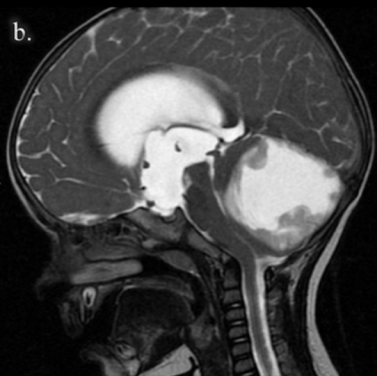
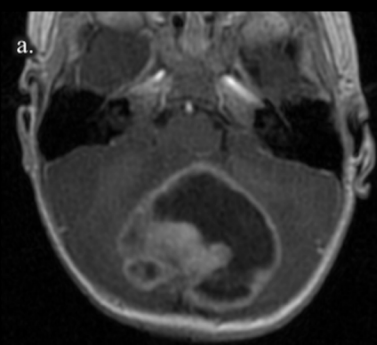
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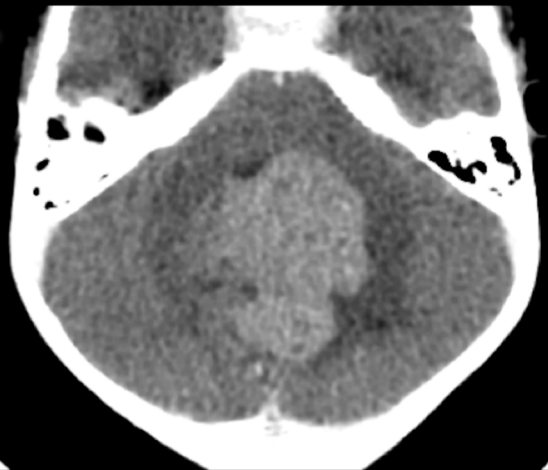
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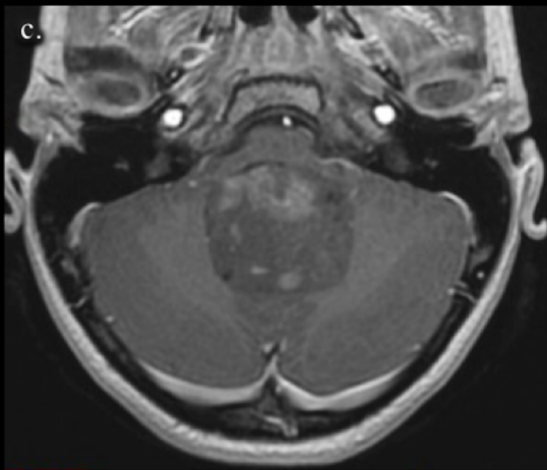
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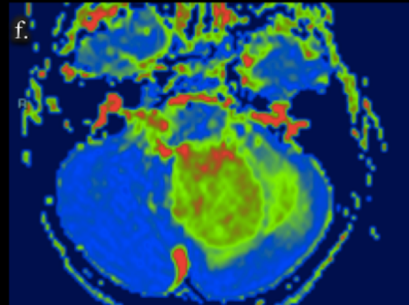
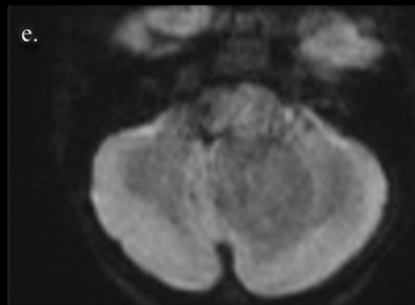
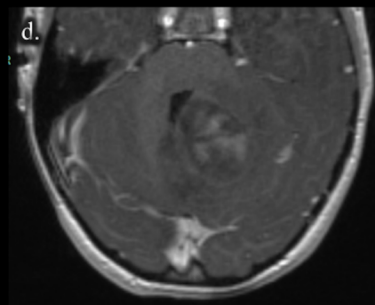
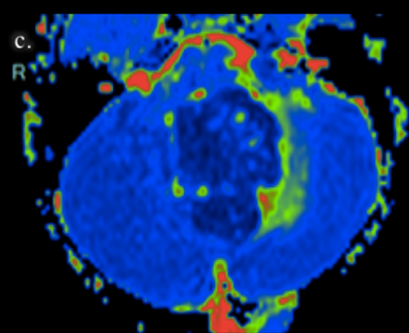
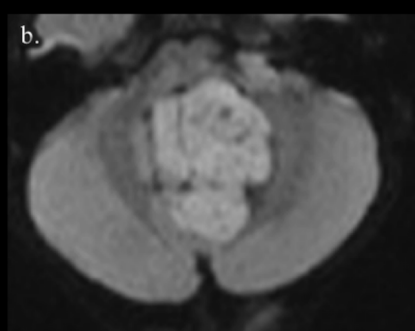


Table 1: Summary of the significant ADC values cut-off and elements in spectroscopy which are useful to discriminate pilocytic astrocytoma, ependymoma and medulloblastoma.

	Embryonal tumors	Ependymoma	Pilocytic astrocytoma
Mean ADC Values Tumor/Brain ADC Ratio	$\leq 0.85 \times 10^{-3} \text{mm}^2$ $\leq 1.2$	between $0.9 - 1.4 \times 10^{-3} \text{mm}^2$ 1.2-1.8	$\geq 1.4 \times 10^{-3} \text{mm}^2$ $\geq 1.8$
Spectroscopy	peak of Taurine at 3.35 ppm	peak of Myo-inositol at 3.5 ppm	decrease of Creatinine at 3.03 ppm