J of Nuclear Medicine Technology, first published online April 19, 2022 as doi:10.2967/jnmt.121.263050

Amino-Acid PET Imaging with ^{18}F-DOPA in the evaluation of Pediatric Brain Tumors

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Running Title: FDOPA and Pediatric Brain Tumors

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The authors have no conflict of interest.

The authors have no financial disclosure.

Study was performed under local IRB approval.

Acknowledgements: We would like to thank Cyclomedical-HMC in facilitating the provision of ^{18}F-DOPA.

I. Abstract

Although MRI is the workhorse of brain tumor initial evaluation and follow-up, there is a growing amount of data recommending the incorporation of amino-acid PET imaging at different stages of the management of these patients. Recent nuclear medicine and neuro-oncology clinical practice recommendations support the use of amino-acid imaging in brain tumor imaging. Considering ^{18}F-DOPA is FDA approved for the evaluation of parkinsonian syndromes, it could be used clinically for other valuable clinical indications such as brain tumor evaluations. This value seems to be well established in adults and has growing evidence for its use in pediatrics as well. We offer to present four pediatric brain tumor cases imaged with ^{18}F-DOPA and review the literature.

Keywords: brain tumors, amino acid imaging, PET, nuclear medicine

II. Introduction

PET has been used in the assessment of brain tumors for 40 years. Nowadays, state of the art MRI has become the gold standard in brain tumor imaging along the various steps of clinical management. ^{18}F-FDG was initially used with some success but faced limitations due to the high background from normal brain glucose metabolism. Amino-acid PET imaging has proven to be superior to ^{18}F-FDG and offers incremental value to MRI in brain tumor imaging. ^{11}Carbon-methyl-L-ethionine (^{11}C-MET), O-(2-[^{18}F]Fluoroethyl)-L-tyrosine (^{18}F-FET) and 3,4-Dihydroxy-6-[^{18}F]fluoro-L-phenylalanine (^{18}F-DOPA) have offered great clinical value. Considering ^{18}F-DOPA is FDA approved for the evaluation of Parkinsonian syndromes and it can be used clinically for other

valuable clinical indications as well. Of note that ^{18}F-Fluciclovine (18F-FACBC, Axumin) is also FDA approved for prostate cancer imaging and is being investigated in brain tumor imaging in adults. Bearing in mind the radiation exposure (albeit minimal) is a matter of concern in pediatrics, amino-acid imaging can be judiciously used in the highest yield case scenarios. We offer to highlight four pediatric brain tumor cases of ^{18}F-DOPA imaging and discuss its main value as well as review amino-acid PET imaging in the pediatric population. Scans were acquired on a 3T MRI and GE Discovery 690 PET-CT scanners at Sidra Medicine. Radiopharmaceutical activities used ranged from 2.7-3.2 mCi.

III. Case Series

Case No 1: A 7 year old boy who was referred to our hospital for visual hallucinations, abdominal pain, headache and seizures. He was diagnosed with temporal lobe epilepsy and had further work-up including a CT and MRI scan of his brain. A well-defined calcified lesion was identified in the right temporal lobe and surgical excision was recommended. His parents were hesitant to consent for surgery. An amino-acid PET imaging using ^{18}F-DOPA was performed for additional prognostic information. The lack of ^{18}F-DOPA uptake by the lesion (**Figure 1**) was indicative of a more benign/low grade process and the parents elected for watchful waiting. Eventually a few months later his parents agreed to surgical excision of the lesion and a right temporal lobe lesionectomy was performed. Histopathology of this lesion revealed meningio-angiomatosis, which is a rare, benign disease of the brain. Lack of ^{18}F-DOPA uptake predicted a benign nature of the lesion and provided additional confidence in the management and reassurance to the family.

Case No 2: A 3 year old boy was evaluated for gait issues and lower extremity weakness. He was then diagnosed with diffuse intrinsic pontine glioma (DIPG). He received standard focal conformal radiotherapy for a total dose of 54 Gy. Eight months after finishing treatment, he presented with mild left sided weakness and limp. He was re-evaluated with an MRI scan that showed his tumor was overall smaller compared to the scan at diagnosis. However there were areas of signal change, which were concerning for disease progression. ^{18}F-DOPA scan in this case showed ^{18}F-DOPA uptake in the area showing contrast enhancement on MRI scan. It was also able to delineate the tumor margins with higher accuracy than MRI and provided an additional negative prognostic indicator in regards to the intensity of ^{18}F-DOPA uptake. **Figure 2**

Case No 3: A 6 year old boy presented with abnormal wide based gait and leg weakness for about 2 months. He then had increased somnolence at school and falls for 3 weeks pre initial diagnosis. He had a brain MRI that demonstrated a midline pontine tumor (DIPG). He similarly received focal radiotherapy for a total dose of 54 Gy. Six months after completing treatment, he presented to the clinic with recurrent gait abnormalities. An MRI scan showed alteration in the internal architectural appearances of the brainstem glioma with marginal dimensional reduction. There were also changes in diffusion weighted imaging patterns between scans that could not be clearly characterized. An ^{18}F-DOPA scan was then performed a few days later and in this case demonstrated tumor viability and recurrence. **Figure 3**

Case No 4: A 3 year old girl presented with a two months history of gait disturbance followed by inability to walk for 3 days prior to her admission to the hospital. An MRI revealed a large posterior fossa tumor which prompted neurosurgical intervention and

resection. Histopathology of the excised specimen revealed anaplastic ependymoma. Immediate post-operative MRI showed a small 8 mm nodule in the resection bed suspicious for residual tumor. Correlative ^{18}F-DOPA PET and MRI performed 3 weeks post-op revealed no uptake in a much smaller nodular density favoring post-operative changes. This obviated the need for second look surgery. **Figure 4**

IV. Discussion

Amino-acid PET imaging has been used successfully for about fifteen years and is gaining in traction in clinical management of brain tumors as several fluorine labelled compounds become more readily available and as data mounts of its major impact on clinical management (1,2,3,4). ^{18}F-DOPA and ^{18}F-FET seem to be the agents with the highest accuracy, although only ^{18}F-DOPA is FDA approved (1,5,6). ^{18}F-DOPA can offer complementary and additive valuable information at different stages of brain tumor management **Figure 5**.

Historically ^{18}F-FDG and ^{11}C-MET, have been used in brain tumor evaluation. Higher FDG uptake has been correlated with higher grade and worse prognosis but is no longer routinely used in the clinic (2, 6). ^{11}C-MET is limited by its short half-life of 20 minutes and is used only in centers with on-site cyclotron. When available, it can provide useful diagnostic and prognostic information(2, 3). ^{18}F-FET and ^{18}F-DOPA radiotracers are newer and significantly superior and have largely taken over brain tumor imaging with PET(3, 4). Most recently, the European Association of Nuclear medicine (EANM), Society of Nuclear Medicine and Nuclear Imaging (SNMMI), European Association of neuro-Oncology (EANO) and Response Assessment in Neuro-Oncology (RANO) published practice guidelines and procedure standards for imaging of

gliomas using PET with radio-labelled amino acids and ^{18}F-FDG (6). These guidelines have consolidated the benefit of PET imaging in the different stages of brain tumor management as described earlier by the PET RANO group (5).

Pirotte's group has, in the past, extensively explored amino-acid imaging in pediatrics and described their experience over 10 years with ^{18}F-FDG and ^{11}C-MET and outlined the value of PET in the pre-surgical, surgical and post-surgical management of 126 pediatric cases(7). In another study Pirotte et al. showed in 85 pediatric brain tumors that ^{18}F-FDG-PET and/or ^{11}C-MET PET guided treatment for cases in which MRI was unable to assist in selecting accurate biopsy targets (35 patients) or to delineate tumors for maximal resection (50 patients)(8). They also showed in 55 children that absence of uptake of ^{11}C-MET had a high accuracy in excluding high-grade tumors and was able to guide conservative management. Increased uptake was also seen in all patients with high-grade tumors(9). Pirotte et al. also concluded in their evaluation of 9 pediatric cases of infiltrative brain tumors that PET and MR co-guidance for accurate stereotactic biopsy of these lesions improved the diagnostic yield, and made it possible to reduce the sampling in high-risk/functional areas and improved the overall quality of therapeutic management (10). The latter strategy is clinically relevant due to the histological heterogeneity of brain tumors(11,12,13). This additional value of PET imaging when compared to MRI alone assessments was also highlighted in another series of 103 pediatric cases(14).

Furthermore, Morana's group have suggested that ^{18}F-DOPA PET when added to the MRI work-up in cases of infiltrative gliomas may offer additional value in diagnosis, prognosis and therapy assessment(15,16,17,18). Other groups have also pointed to the

impact of a positive ^{18}F-DOPA PET scan on overall survival, progression free survival and overall management of adult patients with low grade primary brain tumors and brain tumor recurrence (19,20,21). On the other hand, Morana's group have also highlighted that although ^{18}F-DOPA can aid in differentiating high and low grade brain tumors, one should be cautious as developmental venous anomalies may represent a false positive finding (22). They recommended that all ^{18}F-DOPA PET interpretations should be performed by expert readers and in correlation with the patients MRI (22). This is of greater importance considering the increased prevalence of developmental anomalies in children with intracranial neoplasms (23). These developmental anomalies were associated with neuronal dysfunction in adjacent brain areas as depicted on ^{18}F-FDG PET (24). Morana et al. also reported on the possibility of seeing ^{18}F-DOPA changes in the basal ganglia secondary to network changes due to cortical resection that needs to be taken into account when interpreting these PET scans (25). ^{18}F-DOPA PET was also highlighted by Bund et al. to be helpful in the evaluation of 53 non-enhancing brain tumors although this was in an adult patient population (mean age 39) (26). ^{18}F-DOPA PET was able to discriminate between dysembryoplastic neuroepithelial tumor and grade II oligodendroglioma and between low- and high-grade gliomas with no contrast enhancement on MRI (26).

In addition, as the management and classification of brain tumors has been shifting from the plain "high" or "low" grade spectrum and incorporating molecular markers that define distinct biological subtypes with a different clinical course, it seems natural that metabolic imaging may add an additional layer of subcategorizing tumors, stratifying management and altering the course of disease. Suchorska et al. briefly summarized

this paradigm in the context of the new World Health Organization classification 2016 for brain tumors (27). At this moment, it may be difficult to differentiate subtypes based on amino-acid PET imaging (27) however higher ^{18}F-DOPA uptake has been associated with IDH mutation in diffuse grade II and grade III gliomas (28). Although most dynamic data stems from ^{18}F-FET, it seems that current dynamic ^{18}F-DOPA data is a predictor of progression/recurrence and progression free survival. However it does not seem to offer any additional value compared to static parameters such as mean and maximum tumor-to-normal-brain ratios, tumor-to-striatum ratios, and metabolic tumor volume (MTV) (29). Ponisio et al. on the other hand, in their report did not uncover any value to dynamic analysis (30). Furthermore, Ginet et al. in their study demonstrated that dynamic ^{18}F-DOPA PET was able to differentiate the molecular features of newly diagnosed gliomas (i.e. presence or absence of isocitrate dehydrogenase mutation), however static uptake parameters were not (31). Lastly, Piccardo et al. compared advanced MRI features and metabolic information obtained by ^{18}F-DOPA PET in 22 pediatric midline gliomas. They showed that in comparison to advanced MRI techniques such as ADC maps, arterial spin labelling (ASL) perfusion maps and MR spectroscopy, ^{18}F-DOPA PET tumor-to-striatum ratio was the only parameter able to discriminate H3K27M-mutant from wild-type diffuse midline gliomas (DMG) independently from histology (32).

V. Conclusion

Amino-acid imaging with ^{18}F-DOPA is a powerful clinical tool and should be used in agreement with the recent joint guidelines from EANM/EANO/RANO (2019) and the neuro-oncology working group (2016). Wider use and pooling of patient data from multicenter registries would provide even more insight.

VI. Key Points

Question: Is amino acid PET imaging with ^{18}F-DOPA of significant value in pediatric brain tumors?

Pertinent Findings: Amino acid PET imaging with ^{18}F-DOPA offers valuable clinical information in the primary diagnosis, treatment response assessment, pseudo-progression and recurrence applications of pediatric brain tumors. predictor of progression/recurrence and progression free survival.

Implications of Patient Care: Amino acid PET imaging with ^{18}F-DOPA in pediatric brain tumors may change clinical management and improve outcomes.

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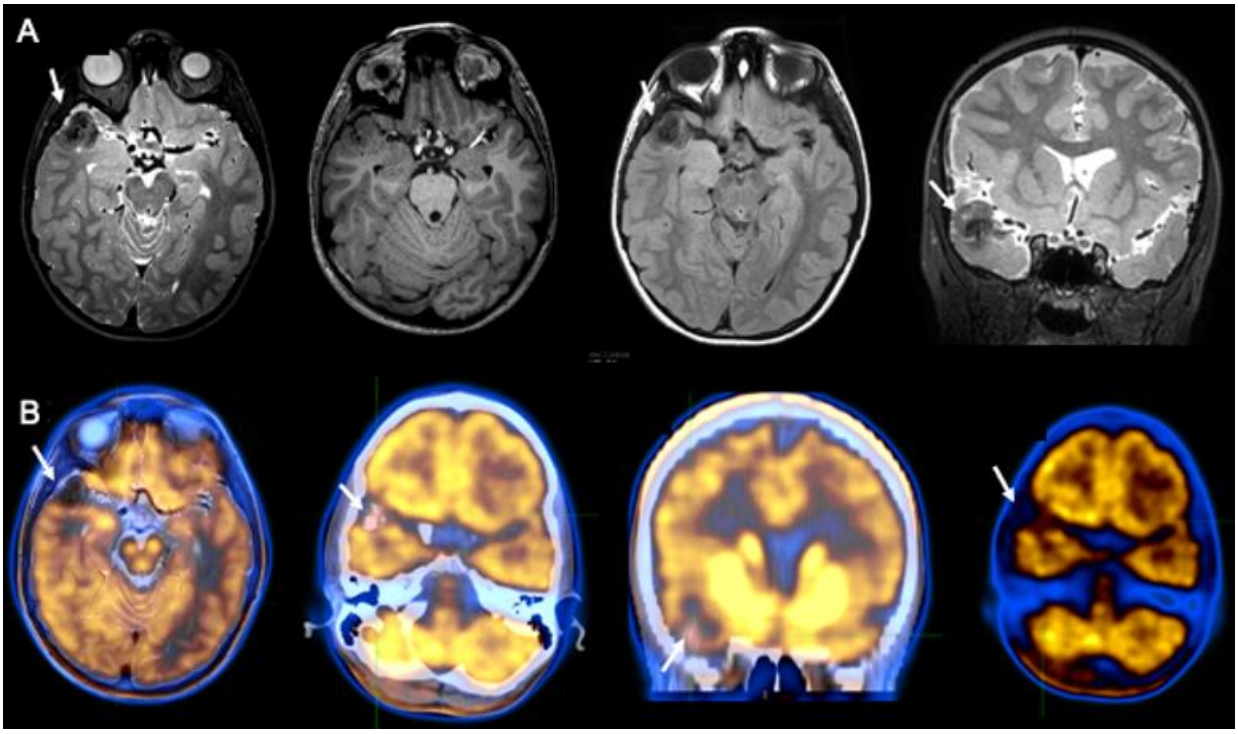

Figure 1. No FDOPA uptake in a calcified benign right temporal lesion (meningio-angiomatosis) (white arrow). **A**. Left to Right: Axial T2, Axial T1, Axial Flair, Coronal T2 **B**. Left to Right: Axial fused FDOPA PET-MR, Axial fused FDOPA PET-CT, Coronal fused FDOPA PET-CT, Axial FDOPA PET image

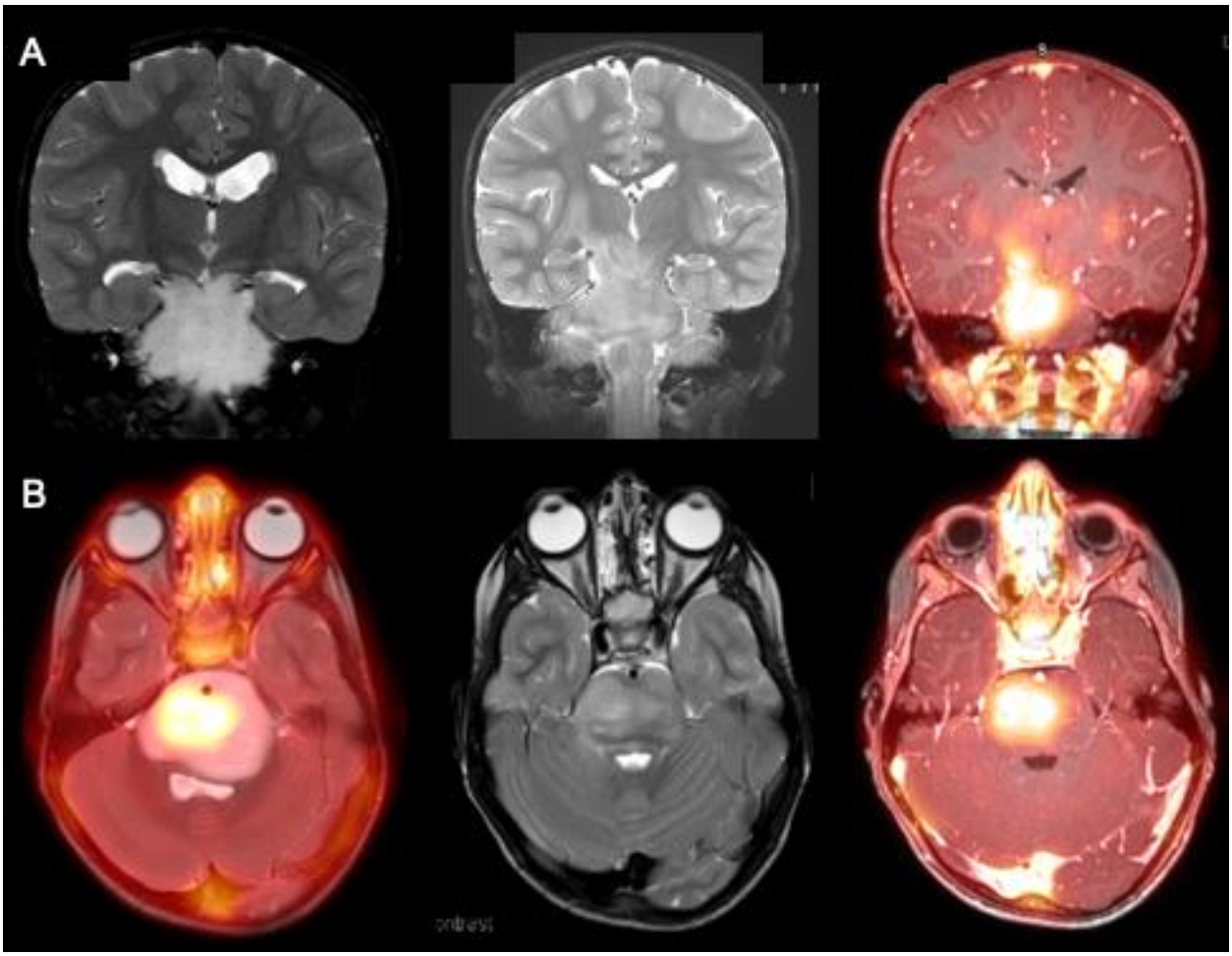

Figure 2. Intense FDOPA uptake in a recurrent DIPG showing better tumor delineation of true tumor boundaries and intensity of uptake likely a prognostic parameter.

A. Left to Right: Coronal T2 FS Initial, Coronal T2 FS 9 M Follow-up (F/U), Coronal Fused FDOPA PET/MR 9 M F/U **B**. Left to Right: Axial FDOPA fused to initial MR, Axial T2 FS 9 M F/U, Axial Fused FDOPA PET/MR 9 M F/U

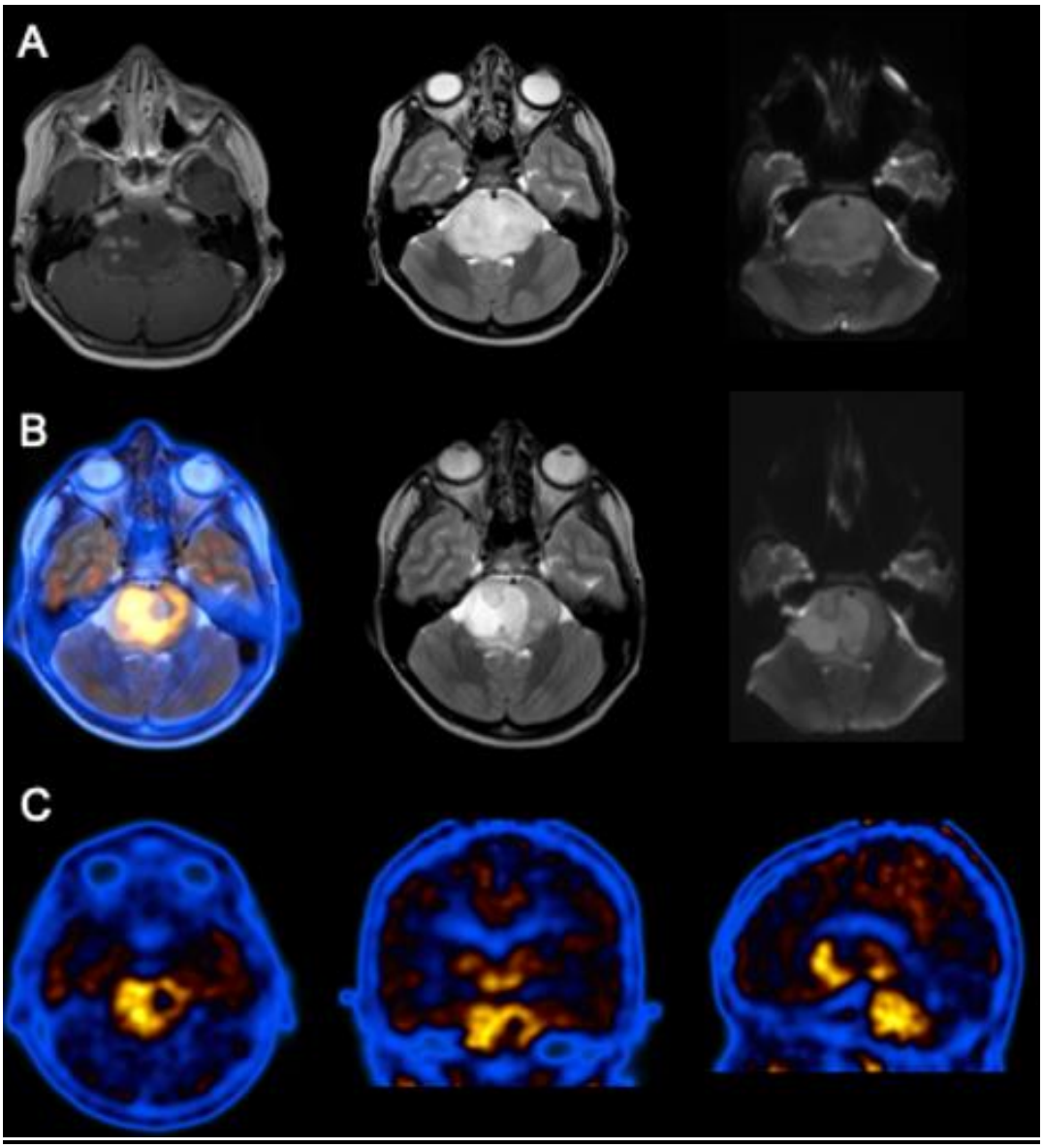

Figure 3. No clear change in the size of the initial DIPG tumor 9 months after the initial MRI. Changes in appearance on different sequences showed T2 and DWI signal distribution changes. FDOPA scan fused with follow up MRI clearly delineates tumor viability and recurrence. **A**. Left to Right: Initial Axial MRI T1 post contrast; Initial Axial MRI T2; Initial Axial DWI. Initial **B**. Axial fused FDOPA PET-MR T2 9 M F/U; Axial MR T2 9 M F/U; Axial DWI 9 M F/U **C**. Axial FDOPA PET; Coronal FDOPA PET; Sagital FDOPA PET

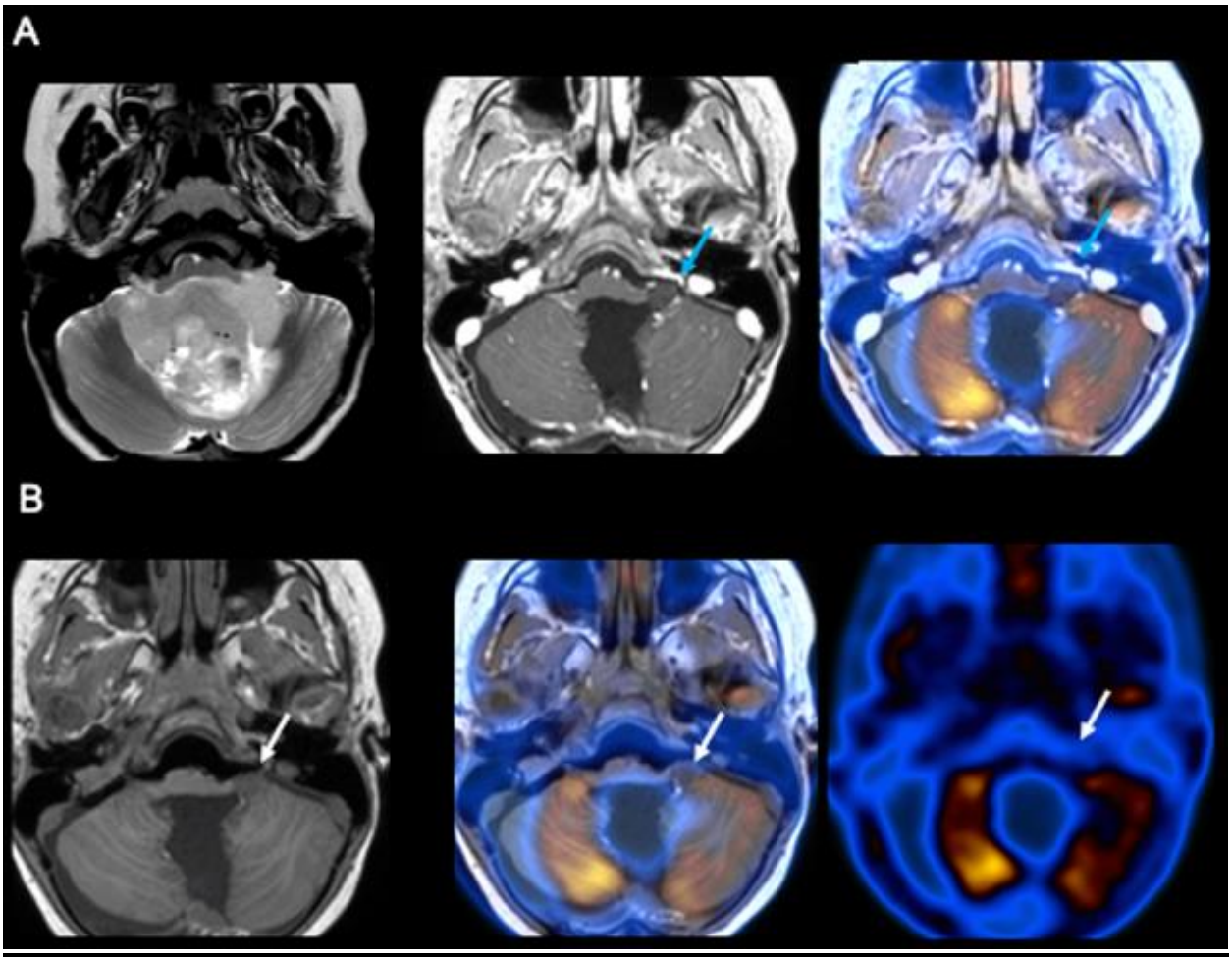

Figure 4. 3 y/o girl status post resection of a posterior fossa tumor (anaplastic ependymoma: World Health Organization grade III) with an immediate post-operative 8 mm left sided nodule (blue arrow) in the resection cavity showing no abnormal FDOPA uptake (3 weeks post-op). Follow-up MRI on same day as the FDOPA scan showed interval reduction in size and near complete resolution of this nodule (white arrow) most consistent with initial postoperative changes. **A**. Left to Right: Axial T2 pre-op MRI; Axial T1 with contrast. Immediate post-op MRI; Axial fused FDOPA PET-Immediate post-op MRI **B**. Left to Right: F/U post-op Axial T1 MRI (3 weeks); Axial fused FDOPA PET-F/U post-op MRI; Axial FDOPA PET

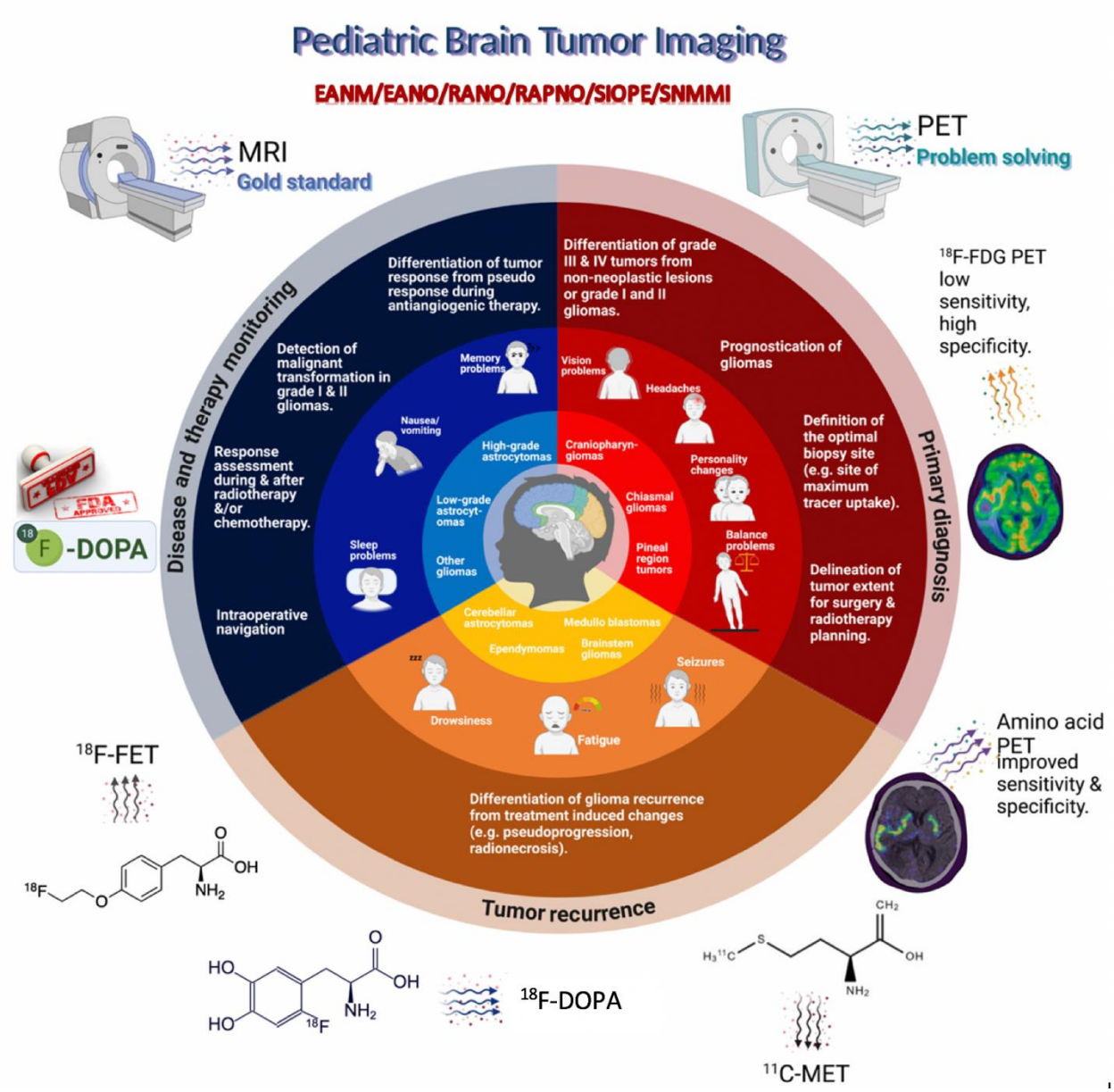

Figure 5: Summary diagram