Published in final edited form as:

Neuroradiology. 2014 May ; 56(5): 405–412. doi:10.1007/s00234-014-1348-9.

“Occult” post-contrast signal enhancement in pediatric diffuse intrinsic pontine glioma is the MRI marker of angiogenesis?

Ashley E. Conway, Wilburn E. Reddick, Yimei Li, Ying Yuan, John O. Glass, Justin N. Baker, Larry Kun, Alberto Broniscer, and Zoltan Patay

Departments of Radiological Sciences (A.E.C., G.W.E., A.S., J.G., Z.P.), Biostatistics (Y.L.), Pediatric Medicine (J.N.B) and Oncology (A.B.) at St. Jude Children’s Research Hospital; Memphis, Tennessee

Abstract

PURPOSE—In diffuse intrinsic pontine gliomas (DIPG), subtracting precontrast from postcontrast T1-weighted images (T1WI) occasionally reveals subtle, “occult” enhancement. We hypothesized that this represents intravascular enhancement related to angiogenesis and hence that these tumors should have greater blood volume fractions than do non-enhancing tumors.

METHODS—We retrospectively screened MR images of 66 patients initially diagnosed with DIPG and analyzed pretreatment conventional and dynamic susceptibility contrast (DSC) perfusion-MRI studies of 61 patients. To determine the incidence of occult enhancement, cerebral blood volume values were compared in areas of occult enhancement (OcE), no enhancement (NE), and normal-appearing deep cerebellar white matter (DCWM).

RESULTS—Tumors of 10 patients (16.4%) had occult enhancement; those of 6 patients (9.8%) had no enhancement at all. The average cerebral blood volume in areas of occult enhancement was significantly higher than that in non-enhancing areas of the same tumor ($P=.03$), within DCWM in the same patient ($P=.03$), and when compared to anatomically paired/similar regions of interest (ROI)s in patients with non-enhancing tumors ($P=.005$).

CONCLUSIONS—Areas of OcE correspond to areas of higher CBV in DIPG, which may be an MRI marker for angiogenesis, but larger scale studies may be needed to determine its potential relevance to grading by imaging, treatment stratification, biopsy guidance, and evaluation of response to targeted therapy.

Keywords

diffuse intrinsic pontine glioma; perfusion imaging; cerebral blood volume; magnetic resonance imaging

Introduction

Approximately 11% of central nervous system (CNS) tumors in children are brainstem tumors,[1] nearly 80% of which are DIPGs, neoplasms associated with a dismal prognosis despite continued efforts to develop novel treatment strategies.[2] Available literature suggests that many of these neoplasms are actually high-grade (i.e., WHO grade 3 or 4) at diagnosis, and virtually all are glioblastoma multiforme at autopsy.[3–5] Because the conventional MRI features of DIPGs are considered to be virtually pathognomonic and the prognosis is nearly uniformly poor, the use of biopsy for histologic confirmation remains controversial.[6, 5, 7, 8] Therefore, identifying robust imaging biomarkers at the time of diagnosis that may indicate earlier or more advanced stages of the disease or different biological properties and correlating these features? with outcome measures may have value for staging, therapeutic stratification, and prognostication.

One such imaging biomarker in tumors of the CNS (including DIPG) is signal enhancement on T1WIs after IV injection of gadolinium-based contrast agents. Inconsistent positive correlation between signal enhancement and histological tumor grade is well recognized in supratentorial gliomas.[9] In DIPGs specifically, a retrospective review evaluating the use of conventional MRI techniques to predict outcomes specifically found no prognostic significance of any conventional MRI features, including classic, overt enhancement (OvE) [10], but another conflicting report of a larger study suggests an association between OvE and poor outcome measures.[11] Therefore, the correlation of OvE with DIPG outcome is currently still controversial.

We have occasionally observed a peculiar type of contrast enhancement in various cerebral neoplasms, including DIPGs, when precontrast T1WIs are subtracted from postcontrast T1WIs. This subtle, web-like enhancement pattern that we refer to as “occult” (hidden) enhancement (OcE) has not been reported in DIPGs or other brain tumors. We hypothesized that the histopathological substrate of OcE is early angiogenesis induced by tumor hypoxia rather than disruption of the blood-brain barrier (BBB), which is classically represented by OvE and typically associated with more advanced stages of the disease. If this is the case, then tumors showing OcE should be characterized by a cerebral blood volume (CBV) which is higher than that of non-enhancing (NE) tumors.

Patients and Methods

Patient accrual

This retrospective review of clinical and MRI data was approved by the Institutional Review Board. A parent or legal guardian of each patient gave informed consent prior to enrollment into the applicable clinical therapeutic trials and protocol-based imaging studies.

Pretreatment baseline MR images of 66 patients initially diagnosed with DIPG (35 boys, 31 girls; median age at diagnosis 6.3 years, range 2.3–17.3 years) and enrolled in phase 1 and phase 2 treatment protocols at our institution from May 2007 through May 2011 were retrospectively reviewed for the presence of OcE on T1-weighted subtraction images. To limit the review to “classic” DIPGs, the 5 patients with atypical imaging or clinical features

such as a.) significant extrapontine extension, suggestive of gliomatosis cerebri (n=2), b.) tumor confined to the brainstem but not originating in the pons (n=1), or c.) overall survival (OS) greater than 3 years (n=2), were excluded from our review.

MR Imaging

All but 4 MRI examinations were performed using a 3T magnet (Siemens Trio, Siemens Medical Systems, Malvern, PA), and all were performed while the patient was under sedation or general anesthesia. The standard conventional imaging protocols included the following sequences: sagittal T1-weighted gradient-echo (TR:215 ms, TE:2.22ms, flip angle:70), axial T1-weighted gradient-echo (TR:224 ms, TE:2.31 ms, flip angle:70), sagittal 3D T2-weighted (TR:3000 ms, TE:3.46 ms), axial T2-weighted fast spin-echo (TR:7960 ms, TE:83 ms, flip angle:180), axial susceptibility-weighted (TR:27 ms, TE:20 ms, flip angle:15), axial echo-planar diffusion-weighted (TR:4800 ms, TE:78 ms), gadolinium-enhanced sagittal 3D T1-weighted (TR:1560 ms, TE:2.15 ms, flip angle:15), axial T1-weighted, coronal T1-weighted gradient-echo (TR:233 ms, TE:2.22 ms, flip angle:70) and axial FLAIR (TR:10000 ms, TE:103 ms, flip angle:130). A gadolinium-based contrast agent (Magnevist, Bayer HealthCare Pharmaceuticals, Wayne, NJ) was used for contrast-enhanced imaging at an aggregate standard dose of 0.1 mmol/kg.

DSC perfusion images were acquired with an axial echo-planar gradient-echo sequence (TR: 1800–1980 ms, TE: 28 or 50 ms, flip angle: 90, 1 average). as 15 contiguous sections (each 4 mm thick) of the entire brainstem and portions of the supratentorial brain and with a 256-square matrix to match the resolution of the conventional imaging. For preloading, 0.1 mL/kg IV gadolinium-based contrast agent was used. After 5 minutes, 50 image sets having a temporal sampling of 2 seconds were acquired during IV bolus reinjection of 0.1 mL/kg contrast followed by a 20-mL saline flush, both delivered by a power injector at the rate of 1–2 mL/s (depending on the maximum psi/flow rates recommended by the manufacturer of the IV line/port used in a given patient).

Analysis of perfusion data

OcE was defined as being a subtle, web-like signal enhancement that was unequivocally identified when pre-contrast T1WIs were subtracted from post-contrast T1WIs but that could not confidently be appreciated on post-contrast T1WIs without subtraction of the pre-contrast T1WIs. DSC perfusion MRI data analysis was attempted for the 10 patients identified as having tumors with OcE on T1-subtraction images, but studies from 4 of those had to be excluded because of technical issues with data acquisition (n=2) or the presence of hemorrhage that generated inherent susceptibility artifacts in the OcE area (n=2). All 6 patients who had no enhancement, even on T1-weighted subtraction images, served as controls.

Because processing the perfusion imaging dataset to determine the brain's hemodynamic parameters relies heavily on the arterial input function, an iterative automated process using a Kohonen self-organizing map was used to identify the arterial input function from a constrained set of images at the level of the basilar artery. Then, perfusion imaging sets were analyzed by a truncated single-value deconvolution combined with a standard-form

Tikhonov regularization with generalized cross-validation to yield parametric maps of CBV, flow, and mean transit times for all slices in the perfusion imaging set. Perfusion maps were then registered onto the T2 image with a nonlinear registration of local deformations by using a free-form deformation based on B-spline interpolation[12].

Spatial normalization of the perfusion data was successful for 10 of 12 patients' images (4 of 6 with OcE and all 6 with no enhancement). For the 2 patients with OcE but without satisfactory spatial normalization, ROIs were placed directly on the perfusion image by using the corresponding T1-weighted subtraction image and T1WI for guidance. ROIs were then transferred from T1-subtraction images to perfusion maps, and CBV values were extracted.

A standard ROI (20 × 20 pixels) was drawn on axial T1-subtraction images of the 4 patients with OcE and successful spatial normalization by using ImageJ (National Institutes of Health) to sample OcE tumor, NE tumor, and DCWM: the latter represented normal parenchyma for referencing purposes. All ROIs were drawn by two reviewers, and final group assignments were decided by consensus. Identical ROIs were placed, preferably in anatomically corresponding tumor areas, in the NE control group to account for possible physiologic variations in brainstem vascularity. Representative ROIs are shown in Figure 1. Areas of necrosis or hemorrhage were avoided. Whenever possible, ROIs of patients with OcE were placed on the slice with the most obvious OcE area. However, ROIs were sometimes placed on an adjacent slice to avoid one or more sizeable (i.e. visible on subtraction images) intratumoral vessels which would "contaminate" the ROI. For unilateral OcE areas, the DCWM ROI was placed ipsilaterally to the OcE area. We also determined relative CBV (rCBV) values for both OcE and NE tumor areas, calculating CBV values relative to the internal standard, notably the normal-appearing DCWM. In our cases, this meant $rCBV_{OcE} = CBV_{OcE} / CBV_{DCWM}$ and $rCBV = CBV_{NE} / CBV_{DCWM}$.

Statistical Evaluation

The Wilcoxon rank sum test was used to test the following: (1) whether the average CBV of patients with OcE was the same as that of those with NE; (2) whether the average CBVs extracted from OcE ROIs, NE ROIs, and DCWM ROIs were different within the OcE group; (3) whether the average rCBV was higher in areas of OcE than in NE areas of the same tumor; (4) whether the average rCBV within tumors of patients with no tumor enhancement was lower than that in areas of OcE in patients with OcE tumors; and (5) whether the average rCBV within tumors of patients with no tumor enhancement was different from that in NE areas of patients with OcE tumors. The Fisher's exact test was used to evaluate treatment randomization between the OcE and NE groups. All statistical analyses were performed by using SAS version 9.2 (SAS Institute, Cary, NC). Statistical significance was assumed when $P < .05$.

Results

Patient Demographics and Conventional Imaging Findings

Of the 61 patients with typical DIPG (32 girls, 29 boys; median age at diagnosis 6.2 years, range 2.3–17.3 years), 45 (73.8%) had tumors with OvE. A total of 10 (16.4%) had tumors with OcE, and only 6 (9.8%) had tumors with no enhancement on the initial MRI workup (see definition of OcE and NE in the Methods section).

Perfusion Analysis

CBV values of each ROI in each patient with either OcE or NE tumors who was included in perfusion analysis are shown in Tables 1 and 2, respectively. Within the OcE group, the average CBV and average rCBV in areas of OcE was significantly higher than in NE areas of the same tumor (CBV $P = .0313$, rCBV $P = .0313$). This was also true for average CBV in DCWM ($P = .0313$) (Tables 3 and 5).

Between the OcE and NE groups, both average CBV and average rCBV were significantly higher in OcE areas than in anatomically corresponding tumor areas in patients with no enhancement (CBV $P = .0051$; rCBV $P = .0131$) (Table 4 and 6). The average CBVs in NE and DCWM ROIs were higher in the OcE group than in the NE group, but not significantly (NE ROIs, $P = .13$; DCWM ROIs, $P = .18$) (Table 4).

Discussion

To the best of our knowledge, subtraction positive, OcE in cerebral neoplasms has not been previously described in the literature. In this report we provide a definition for this relatively rare MRI semiological sign, report its incidence in DIPG and using DSC perfusion analysis we propose an interpretation of the phenomenon in histopathological terms. Indeed, our data suggest that “subtraction positive”, OcE in DIPG may be an MRI marker for angiogenesis.

A previous report of a smaller cohort of patients with DIPG found OvE in 51% of baseline diagnostic MRI studies[10]. Our cohort had a higher percentage of tumors with OvE, and more than half of those without apparent enhancement had OcE, suggesting that some form of enhancement (overt or occult) is more common (90.2%) than previously documented and that only a small percentage of DIPG patients may actually have completely NE tumors at the time of initial diagnosis.

The classic OvE pattern predominantly results from the extravasation of the IV-administered contrast agent through a disrupted BBB of eroded or newly formed, “imperfect”, leaky microvasculature. OvE is often associated with higher histological grade in cerebral gliomas; however, it is also well known that the absence of OvE does not necessarily indicate low histological grade.[13–16]

Angiogenesis is necessary for tumor growth,[14] and the process of angiogenesis in response to tumor hypoxia in glioblastoma multiforme has been well described.[13, 17–19] The relationship between increased vascularity (i.e., angiogenesis) and elevated CBV in adult supratentorial gliomas is well-established too.[20–23] Our finding of significantly

higher CBVs in areas of OcE supports our hypothesis that OcE indicates early, regional expansion of the intravascular compartment and, thus, local angiogenic response to hypoxia, which at that stage is not yet associated with classically defined significant BBB insufficiency. In our patients, all individual CBV values extracted from OcE areas were above the average CBV values of NE tumor areas and DCWM of both the OcE and NE groups, suggesting that OcE is associated with increased CBV and is a reliable and robust conventional MRI marker of angiogenesis, which may be evaluated on routine contrast-enhanced MRI studies in all clinical settings.

Data in the literature about the potential prognostic value of OvE in DIPG are controversial. Previous reports suggested that OvE was not a prognostic marker in DIPG.[10, 24, 25] Conversely, a study of 106 children with DIPG enrolled in clinical trials showed that OvE at baseline was associated with poorer progression-free survival and OS.[11]

The role of DSC perfusion MRI in the characterization of some other cerebral gliomas is better established. In adult supratentorial gliomas, increased rCBV is widely recognized as being a more robust predictor of outcome than is histopathological grade. Although several rCBV cut-off values to predict poor or more favorable outcome without histopathological grading have been published, the most widely accepted is that of 1.75, proposed by Law et al. [9] Increased rCBV values in DIPG were found to be associated with poorer outcome in one study.[26] This study, however, was based on non-quantitative CBV analysis.

Because in our cohort the average rCBV values in areas of OcE were above the 1.75 threshold, it is conceivable that DIPGs and other tumors with OcE may be associated with poorer outcomes than would those with no enhancement at all. However, whether rCBV threshold values established in adult supratentorial gliomas are appropriate for evaluating pediatric infratentorial gliomas, and if rCBV values have similar prognostic value in DIPG will require further study powered for survival analysis. The possibility of additional prognostic differences between OcE and OvE needs to be examined as well.

We recognize that our study has limitations. First, although the relationship between CBV and increased vascularity is well-established in adult supratentorial gliomas, histologic verification was not possible in this study. Molecular biology data however suggest that some features in adult gliomas may not be directly applicable to DIPGs.[27] Second, because the purpose of this study was to investigate the perfusion properties of a particular form of contrast enhancement, we did not investigate the global perfusion properties of each tumor or, for example, explore the possibility of increased CBV in NE areas of tumors otherwise exhibiting OvE. Despite these limitations, our study may have clinical implications. As our understanding of DIPG advances, genetic and molecular information obtainable only by biopsy may become increasingly pertinent for identifying different stages or subtypes of the disease that have potential relevance to prognostication and the likelihood of tumor response to specific targeted therapies [28–31] re-introducing a role for histopathological confirmation and perhaps molecular biological characterization in the diagnosis of DIPG. In conventional MR images, most DIPGs show obvious inhomogeneities within the tumor field. The signal intensity variations likely correspond with histopathological changes such as hypercellularity,[32] hemorrhage,[33] necrosis, and

edema. In fact, the potential usefulness and feasibility of using advanced MRI techniques for regional analysis of the tumor field has been shown for T2-hypointense foci characterized by decreased diffusion properties and increased CBV, which together seem to serve as surrogate imaging markers for foci of anaplasia and, therefore, for higher histopathological grade.[32] The ability to properly identify tumor regions harboring the highest-grade features for targeted biopsy may optimize grading..[34] Because hypoxia-induced angiogenesis likely occurs in areas of high tumor cell density and increased metabolic needs, we believe that OcE may represent a useful stereotactic biopsy site,[32] especially if associated with other MRI indicators of anaplasia. Furthermore, response to therapies targeting vascular endothelial growth factor receptors may also be optimally evaluated by monitoring rCBV and other perfusion metric changes in areas of OcE.

Conclusions

Because the increased CBV in areas of OcE is likely a result of angiogenic expansion of the intravascular blood compartment within the tumor, our findings suggest that OcE may indeed be an MRI marker for hypoxia-induced angiogenesis in DIPG and, perhaps, in other cerebral neoplasms. OcE is an underappreciated form of contrast enhancement; hence, the incidence of contrast enhancement in DIPGs has likely been underestimated because OcE was not included in previous estimates. Clinically, OcE may be relevant for identifying a candidate stereotactic biopsy site for histopathological tumor characterization and provide opportunities to monitor the efficacy of antiangiogenic therapies.

Acknowledgments

The authors thank Suzanne Gronemeyer, PhD, and the St. Jude Pediatric Oncology Education Program for supporting this work and Cherise M. Guess, PhD, ELS, of St. Jude Children's Research Hospital's Scientific Editing Department for reviewing and editing the manuscript.

This work was supported in part by Cancer Center Support (CORE) Grant (P30 CA21765) and 5R25CA02394 (to A.E.C.) from the National Cancer Institute and the American Lebanese Syrian Associated Charities (ALSAC).

REFERENCES

1. CBTRUS Central Brain Tumor Registry of the United States. CBTRUS Statistical Report: Primary brain and central nervous system tumors diagnosed in the United States 2004-2007. 2011 Feb.
2. Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children: critical review of clinical trials. *The Lancet Oncology*. 2006; 7(3):241-248. [PubMed: 16510333]
3. Mantravadi RV, Phatak R, Bellur S, Liebner EJ, Haas R. Brain stem gliomas: an autopsy study of 25 cases. *Cancer*. 1982; 49(6):1294-1296. [PubMed: 6277461]
4. Yoshimura J, Onda K, Tanaka R, Takahashi H. Clinicopathological study of diffuse type brainstem gliomas: analysis of 40 autopsy cases. *Neurol Med Chir (Tokyo)*. 2003; 43(8):375-382. discussion 382. [PubMed: 12968803]
5. Roujeau T, Machado G, Garnett MR, Miquel C, Puget S, Georger B, Grill J, Boddaert N, Di Rocco F, Zerah M, Sainte-Rose C. Stereotactic biopsy of diffuse pontine lesions in children. *J Neurosurg*. 2007; 107(1 Suppl):1-4. [PubMed: 17647306]
6. Schumacher M, Schulte-Monting J, Stoeter P, Warmuth-Metz M, Solymosi L. Magnetic resonance imaging compared with biopsy in the diagnosis of brainstem diseases of childhood: a multicenter review. *J Neurosurg*. 2007; 106(2 Suppl):111-119. [PubMed: 17330536]
7. Leach PA, Estlin EJ, Coope DJ, Thorne JA, Kamaly-Asl ID. Diffuse brainstem gliomas in children: should we or shouldn't we biopsy? *Br J Neurosurg*. 2008; 22(5):619-624. [PubMed: 19016112]

8. Hankinson TC, Campagna EJ, Foreman NK, Handler MH. Interpretation of magnetic resonance images in diffuse intrinsic pontine glioma: a survey of pediatric neurosurgeons. *J Neurosurg Pediatr.* 2011; 8(1):97–102. [PubMed: 21721895]
9. Law M, Yang S, Wang H, Babb JS, Johnson G, Cha S, Knopp EA, Zagzag D. Glioma grading: sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging. *AJNR Am J Neuroradiol.* 2003; 24(10):1989–1998. [PubMed: 14625221]
10. Hargrave D, Chuang N, Bouffet E. Conventional MRI cannot predict survival in childhood diffuse intrinsic pontine glioma. *J Neurooncol.* 2007; 86(3):313–319. [PubMed: 17909941]
11. Poussaint TY, Kocak M, Vajapeyam S, Packer RI, Robertson RL, Geyer R, Haas-Kogan D, Pollack IF, Vezina G, Zimmerman R, Cha S, Patay Z, Boyett JM, Kun LE. MRI as a central component of clinical trials analysis in brainstem glioma: a report from the Pediatric Brain Tumor Consortium (PBTC). *Neuro Oncol.* 2011; 13(4):417–427. [PubMed: 21297126]
12. Rueckert D FA, Schnabel JA. Automatic construction of 3-D statistical deformation models of the brain using nonrigid registration. *IEEE Trans Med Imaging.* 2003; 22:1014–1025. [PubMed: 12906255]
13. Brat DJ, Van Meir EG. Vaso-occlusive and prothrombotic mechanisms associated with tumor hypoxia, necrosis, and accelerated growth in glioblastoma. *Lab Invest.* 2004; 84(4):397–405. [PubMed: 14990981]
14. Folkman J. The role of angiogenesis in tumor growth. *Semin Cancer Biol.* 1992; 3(2):65–71. [PubMed: 1378311]
15. Jain R, Gutierrez J, Narang J, Scarpace L, Schultz LR, Lemke N, Patel SC, Mikkelsen T, Rock JP. In Vivo Correlation of Tumor Blood Volume and Permeability with Histologic and Molecular Angiogenic Markers in Gliomas. *American Journal of Neuroradiology.* 2010; 32(2):388–394. [PubMed: 21071537]
16. Scott JN, Brasher PM, Sevvick RJ, Rewcastle NB, Forsyth PA. How often are nonenhancing supratentorial gliomas malignant? A population study. *Neurology.* 2002; 59(6):947–949. [PubMed: 12297589]
17. Rong Y, Durden DL, Van Meir EG, Brat DJ. 'Pseudopalisading' necrosis in glioblastoma: a familiar morphologic feature that links vascular pathology, hypoxia, and angiogenesis. *J Neuropathol Exp Neurol.* 2006; 65(6):529–539. [PubMed: 16783163]
18. Semenza GL. Vasculogenesis, angiogenesis, and arteriogenesis: mechanisms of blood vessel formation and remodeling. *J Cell Biochem.* 2007; 102(4):840–847. [PubMed: 17891779]
19. Kaur B, Khwaja FW, Severson EA, Matheny SL, Brat DJ, Van Meir EG. Hypoxia and the hypoxia-inducible-factor pathway in glioma growth and angiogenesis. *Neuro Oncol.* 2005; 7(2):134–153. [PubMed: 15831232]
20. Aronen HJ, Gazit IE, Louis DN, Buchbinder BR, Pardo FS, Weisskoff RM, Harsh GR, Cosgrove GR, Halpern EF, Hochberg FH, et al. Cerebral blood volume maps of gliomas: comparison with tumor grade and histologic findings. *Radiology.* 1994; 191(1):41–51. [PubMed: 8134596]
21. Maia AC Jr, Malheiros SM, da Rocha AJ, da Silva CJ, Gabbai AA, Ferraz FA, Stavale JN. MR cerebral blood volume maps correlated with vascular endothelial growth factor expression and tumor grade in nonenhancing gliomas. *AJNR Am J Neuroradiol.* 2005; 26(4):777–783. [PubMed: 15814920]
22. Sadeghi N, D'Haene N, Decaestecker C, Levivier M, Metens T, Maris C, Wikler D, Baleriaux D, Salmon I, Goldman S. Apparent diffusion coefficient and cerebral blood volume in brain gliomas: relation to tumor cell density and tumor microvessel density based on stereotactic biopsies. *AJNR Am J Neuroradiol.* 2008; 29(3):476–482. [PubMed: 18079184]
23. Hu LS, Eschbacher JM, Dueck AC, Heiserman JE, Liu S, Karis JP, Smith KA, Shapiro WR, Pinnaduwage DS, Coons SW, Nakaji P, Debbins J, Feuerstein BG, Baxter LC. Correlations between Perfusion MR Imaging Cerebral Blood Volume, Microvessel Quantification, and Clinical Outcome Using Stereotactic Analysis in Recurrent High-Grade Glioma. *American Journal of Neuroradiology.* 2011; 33(1):69–76. [PubMed: 22095961]
24. Ueoka DI, Nogueira J, Campos JC, Maranhao Filho P, Ferman S, Lima MA. Brainstem gliomas--retrospective analysis of 86 patients. *J Neurol Sci.* 2009; 281(1–2):20–23. [PubMed: 19345380]

25. Fischbein NJ, Prados MD, Wara W, Russo C, Edwards MS, Barkovich AJ. Radiologic classification of brain stem tumors: correlation of magnetic resonance imaging appearance with clinical outcome. *Pediatr Neurosurg*. 1996; 24(1):9–23. [PubMed: 8817611]
26. Hipp SJ, Steffen-Smith E, Hammoud D, Shih JH, Bent R, Warren KE. Predicting outcome of children with diffuse intrinsic pontine gliomas using multiparametric imaging. *Neuro Oncol*. 2011; 13(8):904–909. [PubMed: 21757444]
27. Paugh BS, Qu C, Jones C, Liu Z, Adamowicz-Brice M, Zhang J, Bax DA, Coyle B, Barrow J, Hargrave D, Lowe J, Gajjar A, Zhao W, Broniscer A, Ellison DW, Grundy RG, Baker SJ. Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. *J Clin Oncol*. 2010; 28(18):3061–3068. [PubMed: 20479398]
28. Broniscer A, Baker JN, Tagen M, Onar-Thomas A, Gilbertson RJ, Davidoff AM, Panandiker AP, Leung W, Chin TK, Stewart CF, Kocak M, Rowland C, Merchant TE, Kaste SC, Gajjar A. Phase I Study of Vandetanib During and After Radiotherapy in Children With Diffuse Intrinsic Pontine Glioma. *Journal of Clinical Oncology*. 2010; 28(31):4762–4768. [PubMed: 20921456]
29. Monje M, Mitra SS, Freret ME, Raveh TB, Kim J, Masek M, Attema JL, Li G, Haddix T, Edwards MS, Fisher PG, Weissman IL, Rowitch DH, Vogel H, Wong AJ, Beachy PA. Hedgehog-responsive candidate cell of origin for diffuse intrinsic pontine glioma. *Proc Natl Acad Sci U S A*. 2011; 108(11):4453–4458. [PubMed: 21368213]
30. Barrow J, Adamowicz-Brice M, Cartmill M, MacArthur D, Lowe J, Robson K, Brundler MA, Walker DA, Coyle B, Grundy R. Homozygous loss of ADAM3A revealed by genome-wide analysis of pediatric high-grade glioma and diffuse intrinsic pontine gliomas. *Neuro Oncol*. 2011; 13(2):212–222. [PubMed: 21138945]
31. Law M, Brodsky JE, Babb J, Rosenblum M, Miller DC, Zagzag D, Gruber ML, Johnson G. High cerebral blood volume in human gliomas predicts deletion of chromosome 1p: Preliminary results of molecular studies in gliomas with elevated perfusion. *J Magn Reson Imaging*. 2007; 25(6): 1113–1119. [PubMed: 17520715]
32. Lobel U, Sedlacik J, Reddick WE, Kocak M, Ji Q, Broniscer A, Hillenbrand CM, Patay Z. Quantitative diffusion-weighted and dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging analysis of T2 hypointense lesion components in pediatric diffuse intrinsic pontine glioma. *AJNR Am J Neuroradiol*. 2011; 32(2):315–322. [PubMed: 21087935]
33. Lobel U, Sedlacik J, Sabin ND, Kocak M, Broniscer A, Hillenbrand CM, Patay Z. Three-dimensional susceptibility-weighted imaging and two-dimensional T2*-weighted gradient-echo imaging of intratumoral hemorrhages in pediatric diffuse intrinsic pontine glioma. *Neuroradiology*. 2010; 52(12):1167–1177. [PubMed: 20878319]
34. Barajas RF Jr, Hodgson JG, Chang JS, Vandenberg SR, Yeh RF, Parsa AT, McDermott MW, Berger MS, Dillon WP, Cha S. Glioblastoma multiforme regional genetic and cellular expression patterns: influence on anatomic and physiologic MR imaging. *Radiology*. 2010; 254(2):564–576. [PubMed: 20093527]

FIG 1. MR imaging of a DIPG with OcE. Pre-contrast (A) and post-contrast (B) T1WI and colored CBV map image from the DSC perfusion MRI study (C). Blue rings encircle representative ROIs drawn in the area of OcE (D), NE tumor (E), and DCWM (F) in these T1-subtraction images.

Table 1

CBV values of patients with tumors harboring areas of OcE

The mean (SD) of all ROIs analyzed within each group are as follows: OcE=8.53 (5.08); DCWM=3.84 (1.85); and NE=3.89 (1.63).

Patient	OcE ROIs			DCWM ROIs			NE ROIs		
	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
1	4.44	0.25	12.25	1.56	0.00	3.85	1.65	0.00	6.90
2	8.29	2.45	16.80	7.21	0.00	26.40	4.11	0.00	10.40
3	6.29	1.75	11.50	3.29	1.35	5.85	3.83	0.20	7.45
4	18.56	9.00	31.50	3.90	0.00	7.90	6.25	0.00	23.40
5	6.38	0.00	12.20	3.48	0.00	8.90	2.61	0.00	9.90
6	7.22	4.15	10.50	3.60	1.70	6.25	4.87	0.65	11.00

Table 2

CBV values of patients with NE tumors

The mean (SD) of all ROIs analyzed within each group are as follows: NE ROI-1s=1.95 (0.71); DCWM ROI=2.53 (1.19); and NE ROI-2s=1.98 (0.86).

Patient	NE ROI-1s			DCWM ROIs			NE ROI-2s		
	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
1	1.84	0.00	10.90	1.55	0.00	7.00	1.99	0.00	7.05
2	2.43	0.00	7.90	1.90	0.00	6.35	2.36	0.00	17.40
3	1.91	0.75	4.15	2.34	0.10	5.10	1.99	0.90	3.35
4	1.16	0.00	3.75	1.57	0.00	6.40	1.41	0.00	6.70
5	3.07	0.00	9.85	4.60	0.00	17.10	3.34	0.00	12.75
6	1.29	0.00	12.15	3.24	0.00	11.95	0.80	0.00	2.40

Table 3

Comparison of average CBV values of various ROIs in patients with tumors harboring areas of OcE (n=6)

Comparison	Difference (SD)	P value
OcE vs. NE	4.64 (3.83)	0.0313
OcE vs. DCWM	4.69 (4.96)	0.0313
NE vs. DCWM	0.047 (1.89)	0.8438

Note: Difference=Mean of average CBV of one ROI in OcE – Mean of average CBV of one ROI in OcE; SD=Standard deviation of the difference.

Table 4

Comparison of average CBV values between OcE (n=6) and NE (n=6) patient groups.

Group	ROI	OcE*				NE			
		Diff(SD)	P value	Diff(SD)	P value	DCWM	P value	Diff(SD)	P value
OcE	OcE	6.58(3.62)	0.0051	6.00(3.69)	0.0082			6.55(3.64)	0.0051
	DCWM	1.89(1.40)	0.0306	1.31(1.55)	0.1753			1.86(1.44)	0.0453
	NE	1.94(1.26)	0.0453	1.35(1.45)	0.1282			1.91(1.30)	0.0453

Note: OcE* indicates ROIs in NE tumors in anatomically corresponding locations with ROIs in areas of OcE in patients with OcE tumors. Diff=Mean of average CBV of one ROI in OcE- Mean of average CBV of one ROI in NE.

Table 5

Comparison of average rCBV values between OcE and NE tumor areas in patients with OcE (n=6) and NE (n=6).

Group	OcE (or OcE* in NE group) area	NE area	OcE (or OcE*) vs. NE	
	Mean(SD)	Mean(SD)	Difference(SD)	P value
OcE	2.42(1.27)	1.08(0.38)	1.33(1.00)	0.0313
NE	0.85(0.33)	0.87(0.38)	-0.027(0.11)	0.5625

Note: OcE* indicates ROIs in NE tumors in anatomically corresponding locations with ROIs in areas of OcE in patients with OcE tumors. Difference=Mean of average CBV of OcE ROI in the OcE (or NE) group - Mean of average CBV of NE ROI in the OcE (or NE) group.

Table 6

Comparison of average rCBV values between ROIs in OcE (n=6) and NE (n=6) patient groups.

Group	NE				
	<i>ROI</i>	<i>OcE*</i>	<i>NE</i>		
		Difference (SD)	<i>P</i> value	Difference (SD)	<i>P</i> value
OcE	<i>OcE</i>	1.57 (0.93)	0.0131	1.54 (0.93)	0.0131
	<i>NE</i>	0.24 (0.36)	0.3785	0.21 (0.38)	0.4712

Note: OcE* indicates ROIs in NE tumors in anatomically corresponding locations with ROIs in areas of OcE in patients with OcE tumors. Difference=Mean of average rCBV of one ROI in OcE- Mean of average rCBV of one ROI in NE; SD=standard deviation of the difference.