Diffuse midline glioma H3 K27M-altered case series

2022

Forty-one cases of childhood Diffuse midline glioma H3 K27-altered were collected at Children's Hospital of Fudan University (39 cases) and Xi'an Children's Hospital (2 cases), from July 2016 to July 2020. The clinical manifestations, imaging data, histopathology, immunohistochemical phenotype and molecular genetics features, tumor size, site and histological grading were evaluated. Among the 41 cases, 21 were males and 20 females, the age of onset was 3-14 years, the average and median age was 7.6 years and 7.0 years, respectively. The tumor sites were brain stem (n=36) and other locations (n=5). The clinical manifestations were dizziness, gait disturbance, and limb weakness, etc. The MRI features were variable. The histology varied from low-grade to high-grade glioma with neuron differentiation. Immunohistochemistry showed that the tumor cells expressed H3K27M, GFAP, and Olig2. Genetic study showed that 76% (16/21) of tumors had H3F3A gene mutation, mostly accompanied by TP53 (62%, 13/21) missense mutation; five tumors (24%, 5/21) had HIST1H3B gene mutation, accompanied by missense mutations in ACVR1 and PI3K pathway-related gene PIK3CA (4/5) and PIK3R1 (1/5) mutations. The prognosis was dismal with only one alive and others died. The average and median overall survival time was 7 months and 4 months, respectively. Cox multivariate regression analysis showed that age, tumor location, radiologically maximum tumor diameter, histologic grading, and surgical methods were not significantly associated with overall survival rate ($P>0.05$). Pediatric diffuse midline gliomas with H3K27 alteration have unique clinicopathological and genetic characteristics. The prognosis is poor. The tumor location and histopathologic grading are not related to prognosis. New specific drugs and comprehensive treatment are needed to improve the prognosis [1)].

2019

Piccardo et al., from Genoa, Italy. retrospectively analyzed 22 pediatric patients with DMG histologically proved and molecularly classified as H3K27M-mutant (12 subjects) and wild-type (10 subjects) who underwent DWI, Proton magnetic resonance spectroscopic imaging, and ASL performed within 2 weeks of 18F-FDOPA PET. DWI-derived relative minimum apparent diffusion coefficient (rADC min), Proton magnetic resonance spectroscopic imaging data choline/N-acetylaspartate (Cho/NAA), choline/creatine (Cho/Cr), and presence of lactate and relative ASL-derived cerebral blood flow max (rCBF max) were compared with 18F-DOPA uptake Tumor/Normal tissue (T/N) and Tumor/Striatum (T/S) ratios, and correlated with histological and molecular features of DMG. Statistics included Pearson's chi-square and Mann-Whitney U tests, Spearman's rank correlation and receiver operating characteristic (ROC) analysis.

The highest degrees of correlation among different techniques were found between T/S, rADC min and Cho/NAA ratio ($p < 0.01$), and between rCBF max and rADC min ($p < 0.01$). Significant differences between histologically classified low- and high-grade DMG, independently of H3K27M-mutation, were found among all imaging techniques ($p \leq 0.02$). Significant differences in terms of rCBF max, rADC min, Cho/NAA and 18F-DOPA uptake were also found between molecularly classified mutant and wild-type DMG ($p \leq 0.02$), even though wild-type DMG included low-grade astrocytomas, not present

among mutant DMG. When comparing only histologically defined high-grade mutant and wild-type DMG, only the 18F-DOPA PET data T/S demonstrated statistically significant differences independently of histology ($p < 0.003$). ROC analysis demonstrated that T/S ratio was the best parameter for differentiating mutant from wild-type DMG (AUC 0.94, $p < 0.001$).

Advanced MRI and 18F-DOPA PET characteristics of DMG depend on histological features; however, 18F-DOPA PET-T/S was the only parameter able to discriminate H3K27M-mutant from wild-type DMG independently of histology [2].

Baseline diffusion or apparent diffusion coefficient (ADC) characteristics have been shown to predict outcome related to DIPG, but the predictive value of post-radiation ADC is less well understood. ADC parametric mapping (FDM) was used to measure radiation-related changes in ADC and compared these metrics to baseline ADC in predicting progression-free survival and overall survival using a large multi-center cohort of DIPG patients (Pediatric Brain Tumor Consortium-PBTC).

MR studies at baseline and post-RT in 95 DIPG patients were obtained and serial quantitative ADC parametric maps were generated from diffusion-weighted imaging based on T2/FLAIR and enhancement regions of interest (ROIs). Metrics assessed included total voxels with: increase in ADC (iADC); decrease in ADC (dADC), no change in ADC (nADC), fraction of voxels with increased ADC (fiADC), fraction of voxels with decreased ADC (fdADC), and the ratio of fiADC and fdADC (fDM Ratio).

A total of 72 patients were included in the final analysis. Tumors with higher fiADC between baseline and the first RT time point showed a trend toward shorter PFS with a hazard ratio of 6.44 (CI 0.79, 52.79, $p = 0.083$). In contrast, tumors with higher log mean ADC at baseline had longer PFS, with a hazard ratio of 0.27 (CI 0.09, 0.82, $p = 0.022$). There was no significant association between fDM derived metrics and overall survival.

Baseline ADC values are a stronger predictor of outcome compared to radiation related ADC changes in pediatric DIPG. We show the feasibility of employing parametric mapping techniques in multi-center studies to quantitate spatially heterogeneous treatment response in pediatric tumors, including DIPG [3].

2017

Meyronet et al., from Lyon analyzed the characteristics of 21 adult H3 K27M-mutant gliomas and compared them with those of 135 adult diffuse gliomas without histone H3 and without isocitrate dehydrogenase (IDH) mutation (IDH/H3 wild type).

The median age at diagnosis in H3 K27M-mutant gliomas was 32 years (range: 18-82 y). All tumors had a midline location (spinal cord n = 6, thalamus n = 5, brainstem n = 5, cerebellum n = 3, hypothalamus n = 1, and pineal region n = 1) and were IDH and BRAF-V600E wild type. The identification of an H3 K27M mutation significantly impacted the diagnosis in 3 patients (14%) for whom the histological aspect initially suggested a diffuse low-grade glioma and in 7 patients (33%) for whom pathological analysis hesitated between a diffuse glioma, ganglioglioma, or pilocytic astrocytoma. Compared with IDH/H3 wild-type gliomas, H3 K27M-mutant gliomas were diagnosed at an earlier age (32 vs 64 y, $P < .001$), always had a midline location (21/21 vs 21/130, $P < .001$), less

frequently had a methylated MGMT promoter (1/21 vs 52/129, P = .002), and lacked EGFR amplification (0/21 vs 26/128, P = .02). The median survival was 19.6 months in H3 K27M-mutant gliomas and 17 months in IDH/H3 wild-type gliomas (P = .3).

In adults, as in children, H3 K27M mutations define a distinct subgroup of IDH wild-type gliomas characterized by a constant midline location, low rate of MGMT promoter methylation, and poor prognosis [4].

2015

130 cases of DIPG biopsies and previous published data, these procedures appear to have a diagnostic yield and morbidity rates similar to those reported for other brain locations (3.9 % of transient morbidity in our series). In addition, the quality and the quantity of the material obtained allow to (1) confirm the diagnosis, (2) reveal that WHO grading was useless to predict outcome, and (3) perform an extended molecular screen, including biomarkers study and the development of preclinical models. Recent studies reveal that DIPG may comprise more than one biological entity and a unique oncogenesis involving mutations never described in other types of cancers, i.e., histones H3 K27M and activin receptor ACVR1.

Stereotactic biopsies of DIPG can be considered as a safe procedure in well-trained neurosurgical teams and could be incorporated in protocols. It is a unique opportunity to integrate DIPG biopsies in clinical practice and use the biology at diagnosis to drive the introduction of innovative targeted therapies, in combination with radiotherapy [5].

2007

A suboccipital, transcerebellar approach was used to obtain biopsy samples in 24 children.

Two patients suffered deficits. Both had a transient (< 2 months) new cranial nerve palsy; one of these patients also experienced an exacerbation of a preoperative hemiparesis. No patient died during the perioperative period. A histological diagnosis was made in all 24 patients as follows: 22 had a malignant infiltrative astrocytoma, one had a low-grade astrocytoma, and one had a pilocytic astrocytoma. The diagnosis of the latter two patients affected the initial treatment after the biopsy.

The findings of this study imply that stereotactic biopsy sampling of a diffuse pontine tumor is a safe procedure, is associated with minimal morbidity, and has a high diagnostic yield. A nonmalignant tumor was identified in two of the 24 patients in whom the imaging findings were characteristic of a malignant infiltrative astrocytoma. With the advent of new treatment protocols, stereotactic biopsy sampling, which would allow specific tumor characterization of diffuse pontine lesions, may become standard [6].

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Li J, Ma YY, Feng J, Zhao D, Ding F, Tian L, Chen R, Zhao R. [Diffuse midline gliomas with H3K27 alteration in children: a clinicopathological analysis of forty-one cases]. Zhonghua Bing Li Xue Za Zhi. 2022 Apr 8;51(4):319-325. Chinese. doi: 10.3760/cma.j.cn112151-20210830-00625. PMID: 35359043.
2)
Piccardo A, Tortora D, Mascelli S, Severino M, Piatelli G, Consales A, Pescetto M, Biassoni V, Schiavello E, Massollo M, Verrico A, Milanaccio C, Garrè ML, Rossi A, Morana G. Advanced MR imaging and (18)F-

DOPA PET characteristics of H3K27M-mutant and wild-type pediatric diffuse midline gliomas. Eur J Nucl Med Mol Imaging. 2019 Apr 27. doi: 10.1007/s00259-019-04333-4. [Epub ahead of print] PubMed PMID: 31030232.

3) Ceschin R, Kocak M, Vajapeyam S, Pollack IF, Onar-Thomas A, Dunkel IJ, Poussaint TY, Panigrahy A. Quantifying radiation therapy response using apparent diffusion coefficient (ADC) parametric mapping of pediatric diffuse intrinsic pontine glioma: a report from the pediatric brain tumor consortium. J Neurooncol. 2019 Feb 27. doi: 10.1007/s11060-019-03133-y. [Epub ahead of print] PubMed PMID: 30810873.

4) Meyronet D, Esteban-Mader M, Bonnet C, Joly MO, Uro-Coste E, Amiel-Benouaich A, Forest F, Rousselot-Denis C, Burel-Vandenbos F, Bourg V, Guyotat J, Fenouil T, Jouvet A, Honnorat J, Ducray F. Characteristics of H3 K27M-mutant gliomas in adults. Neuro Oncol. 2017 Aug 1;19(8):1127-1134. doi: 10.1093/neuonc/now274. PubMed PMID: 28201752; PubMed Central PMCID: PMC5570304.

5) Puget S, Beccaria K, Blauwblomme T, Roujeau T, James S, Grill J, Zerah M, Varlet P, Sainte-Rose C. Biopsy in a series of 130 pediatric diffuse intrinsic Pontine gliomas. Childs Nerv Syst. 2015 Oct;31(10):1773-80. doi: 10.1007/s00381-015-2832-1. Epub 2015 Sep 9. PubMed PMID: 26351229.

6) Roujeau T, Machado G, Garnett MR, Miquel C, Puget S, Geoerger B, Grill J, Boddaert N, Di Rocco F, Zerah M, Sainte-Rose C. Stereotactic biopsy of diffuse pontine lesions in children. J Neurosurg. 2007 Jul;107(1 Suppl):1-4. PubMed PMID: 17647306.