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Current Clinical Practice About Pediatric Midline Gliomas in the Scope of Molecular Era

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ABSTRACT

AIM: To share our clinical experience with surgical and adjuvant treatment strategies followed during the treatment of midline gliomas.

MATERIAL and METHODS: Pediatric patients with midline gliomas who underwent surgery in our clinic between March 2016 and November 2019 were included. Tissue samples were obtained through surgical excision, open biopsy, or stereotactic biopsy. All samples were analyzed for ATRX, BRAFV600E, IDH1/2, H3K27M, and H3G34R mutations, EGFR and PGFRA amplifications, and PTEN loss.

RESULTS: There were 7 (43.8%) female and 9 (56.2%) male pediatric patients in the study. Eight patients had thalamic, 5 patients had pontine, 2 patients had medulla oblongata and one patient had brachium pontis tumors. Presenting symptoms were headache, disequilibrium, ophthalmoplegia, and panic attack. Eleven tumors showed H3K27M mutation and were diagnosed as diffuse midline gliomas. BRAFV600E, ATRX mutations, PTEN loss, and EGFR amplifications were other molecular alterations detected within tumor samples. Patients with H3K27M mutant tumors had a shorter life span. Five patients were enrolled in an ONC201 trial.

CONCLUSION: Although most midline gliomas are not amenable to gross total excision, obtaining tissue samples is mandatory for determining patients' exact diagnoses, tailored treatment plans, and eligibility for clinical trials. Stereotactic biopsy for midline gliomas is a safe and effective method.

KEYWORDS: Midline glioma, ONC201, Stereotactic biopsy, Diffuse glioma, Treatment

INTRODUCTION

Brain tumors are the most common solid tumors in pediatric patients (15). Deep seated tumors including brainstem and thalamic gliomas constitute approximately 10% of all glial tumors in childhood (36). These tumors generally show a diffuse growth pattern which makes complete surgical resection impossible (23). With the integration of tumor genetics into pathological classification systems, the World Health Organization (WHO) classified brainstem and thalamic gliomas within the group of midline gliomas (18). The WHO also declared that midline gliomas frequently harbor H3K27M mutation and that the tumors harboring this mutation are known as diffuse midline gliomas (DMG) (18). These tumors have an unfavorable prognosis with a median survival time of less than 1 year (16). Advancements in tumor molecular biology research has led to targeted treatment strategies and some exciting clinical trials for DMGs (4,19,29,31). In this study we aimed to share our clinical experience regarding midline glial tumors following the release of the new WHO classification of central nervous system tumors in 2016.

MATERIAL and METHODS

This retrospective study was approved by the ethical committee of Acibadem University School of Medicine, Istanbul, Turkey (Date: 02.03.2007, No: 2017-4/2). Sixteen pediatric patients with midline glial tumors who underwent surgery or were biopsied in our clinic between March 2016 and November 2019 were included in the study.

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Midline tumor location was defined as medullary, pontine mesencephalic, and thalamic. Tissue samples were obtained through either surgical excision, open biopsy, or stereotactic biopsy.

All patients had preoperative and postoperative 36th hour cranial magnetic resonance imaging (MRI) with contrast. They also had an early (within 6 hours after surgery) postoperative computerized tomography scan to confirm the surgical excision and/or biopsy site and to rule out early postoperative hemorrhage. They all received chemotherapy (Chx) with one of the standard protocols and all patients received radiation therapy (RT). Some patients also joined a clinical trial after completing the standard Chx and RT.

The pathology specimens of all patients were reviewed by a single neuropathologist. After routine immunohistochemical pathological procedures, all samples were also investigated for BRAFv600E point mutation with real time PCR, IDH1/2, H3K27M and H3G34R with Sanger sequencing, and EGFR amplification, PDGFRA amplification, and PTEN loss with fluorescein in-situ hybridization.

Statistical analysis was performed using SPSS Statistics 20.0 software.

RESULTS

There were 7 (43.8%) female, and 9 (56.2%) male pediatric patients included in the study. The mean age of the patients was 8 years (range 4.7–13.9 years). The mean follow-up time was 18 months (range 1.535.2 months). All patients had brainstem (mesencephalon, pons, and medulla oblongata) and thalamic tumors. Eight (50%) patients had thalamic tumors, 5 (31.25%) patients had pontine tumors, 2 (12.5%) patients had medulla oblongata tumors, and 1 (6.25%) patient had a brachium pontis – cerebellar hemisphere tumor. Three out of 8 patients with thalamic tumors had bi-thalamic tumor involvement. Presenting symptoms were, headache in 2 (12.5%) patients, disequilibrium in 2 (12.5%) patients, both headache and disequilibrium in 3 (18.7%) patients, ophthalmoplegia in 4 (25%) patients, absence seizures in 1 (6.3%) patient, lightheadedness in 1 (6.3%) patient, ophthalmoplegia and balance problems in 2 patients (12.5%), and panic attack in 1(6.3%) patient. The biopsies were obtained by stereotactic biopsy in eight (50%) patients, by near total surgical excision in 4 (25%) patients, by open biopsy in 3 (18.8%) patients, and by endoscopic biopsy in 1 patient (6.2%), who also presented with obstructive hydrocephalus (Figure 1A-I; 2A-F; 3A-D; 4A-D).

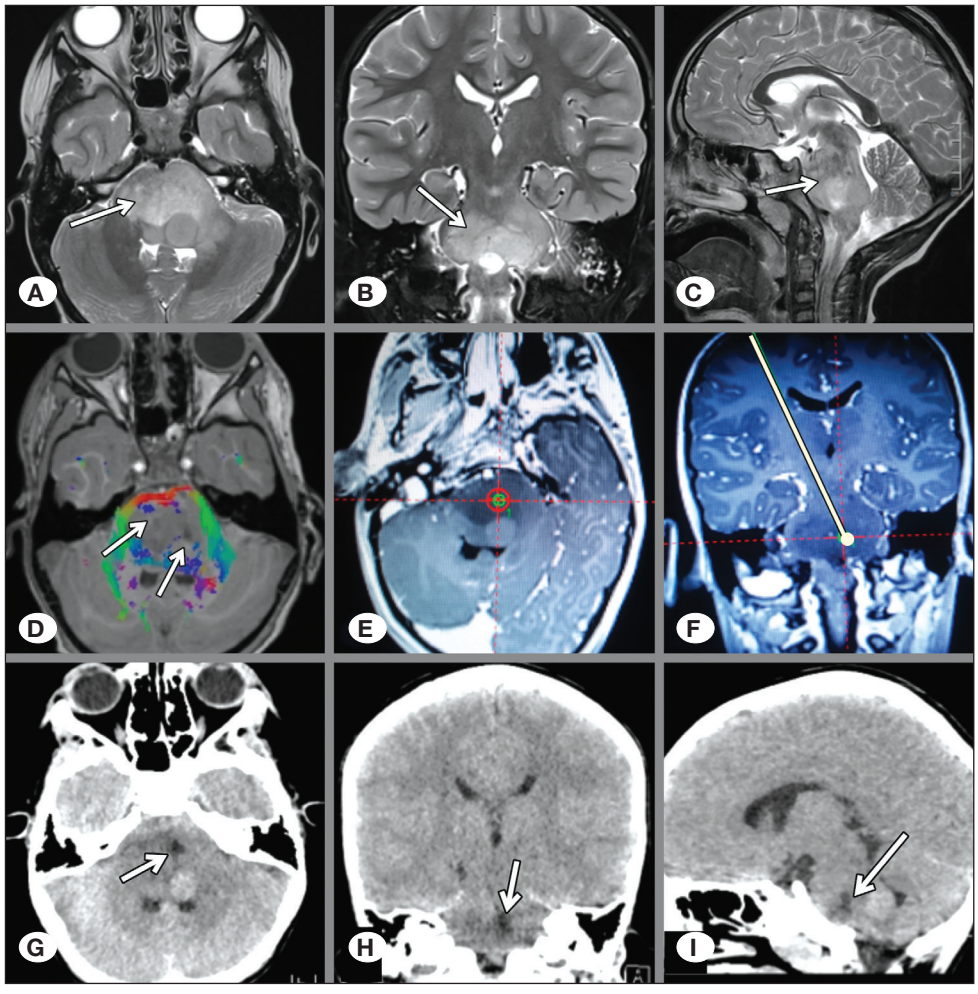

Figure 1: (Case 7) A 5 years old boy presented with ophthalmoplegia. **A,B,C)** Axial, coronal and sagittal section T2 weighted brain MRI shows diffuse midline tumor within pons (arrows). **D)** Axial section tractography shows corticospinal tracts within the tumor tissue. **E)** Axial section MRI on SurgiPlan. Red circle indicates stereotactic biopsy target. **F)** White line designates stereotactic biopsy trajectory. **G,H,I)** Axial, coronal and sagittal section cranial tomography confirms the biopsied region (arrows).

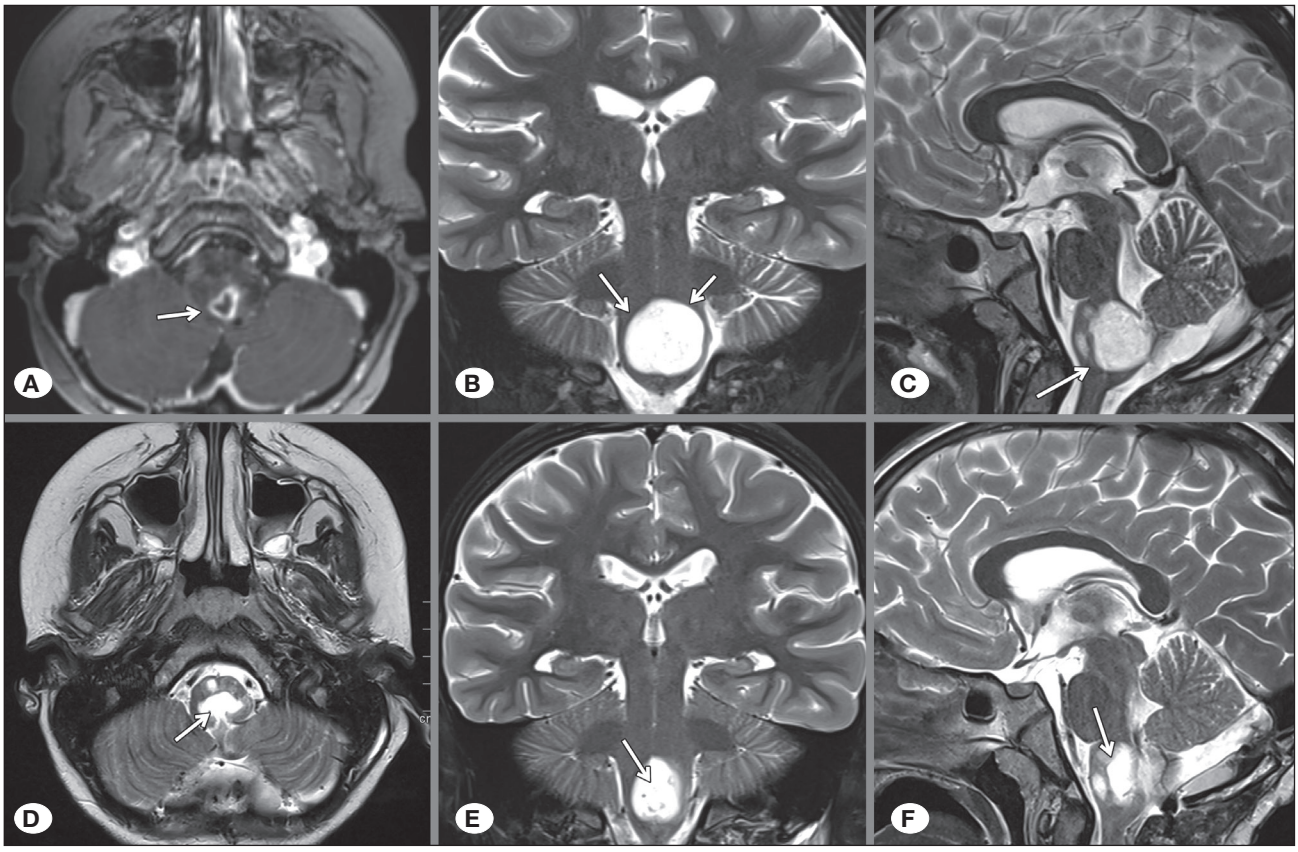

Figure 2: (Case 15) A 9 years old boy presented with disequilibrium. **A)** Axial section contrast enhanced MRI scan revealed a lesion that shows heterogeneous ring contrast enhancement (arrow). **B, C)** Coronal and sagittal section T2 weighted MRI scans shows T2 hyperintense mass lesion at the level of cervico medullary junction. **D,E,F)** Axial, coronal and sagittal section MRI scans shows gross total resection of the lesion (arrows).

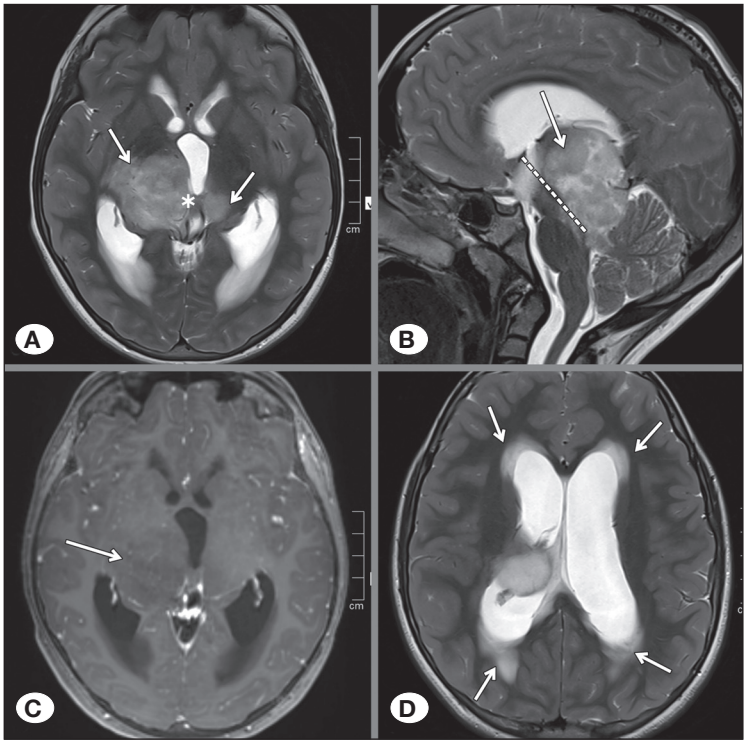

Figure 3: (Case 3) A 9 years old boy present clinic with headache and disequilibrium. **A)** Axial section T2 weighted MRI shows a right sided thalamic mass (arrow) which passed to the contralateral thalamus through the interthalamic adhesion (asterisks). **B)** Sagittal section, T2 weighted MRI shows a huge tumor compresses aqueductus (arrow). Dotted line demonstrates original place of aqueductus Sylvii. **C)** Tumor did not show contrast enhancement on T1 weighted axial images (arrow). **D)** Patient had overt hydrocephalus with dilated ventricles secondary to aqueductal compression. Arrows indicate transependimal cerebrospinal fluid migration. This patient had endoscopic third ventriculostomy operation to relieve hydrocephalus. During endoscopic procedure we also had thalamic biopsy for the morphomolecular diagnosis of the tumor.

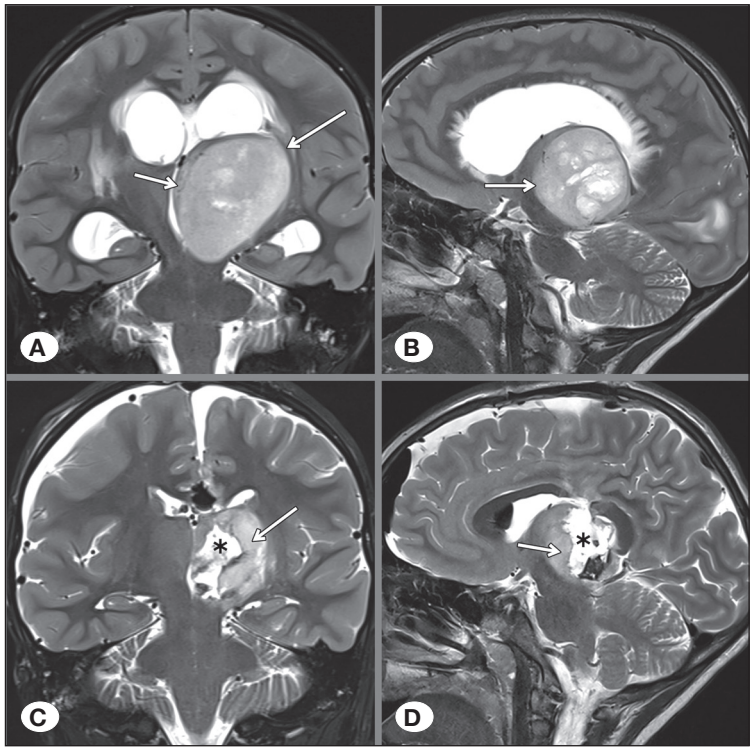

Figure 4: (Case 14) An 8 years old girl presents clinic with headache and disequilibrium and headache.
A, B) Coronal and sagittal sectionT2 weighted MRIs shows left thalamic mass lesion (arrows).
C, D) Since intraoperative pathological diagnosis was consisting with the high grade diffuse glioma, we just decompressed the tumor tissue and left the surrounding tumor not to harm the patient. Coronal and sagittal section T2 weighted MRIs confirms subtotal resection of the tumor. Arrows show tumor tissue, asterisks designates excision cavity.

Immunohistochemical pathology results were consistent with grade 2 diffuse astrocytoma in 8 (50%) patients, and high grade diffuse glioma in 8 (50%) patients. Molecular tests revealed that 11 patients (68.8%) had H3K27M mutation. Five (62.5%) out of 8 thalamic tumors, 1 (50%) of 2 medulla oblongata tumors, 4 (80%) of 5 pontine tumors, and the only one cerebellar tumor within the cohort exhibited H3K27M mutation. All tumors that had H3K27M mutation were named as 'DMG' after the Sanger sequencing results were received. The histopathological diagnosis of 5 (31.2%) patients who had a previous diagnosis of diffuse astrocytoma grade 2 was revised as high grade diffuse glial tumor since they harbor H3K27M mutation. Other molecular alterations that were obtained during molecular analysis were BRAFV600E and ATRX(with immunohistochemistry) mutations, PTEN loss, and EGFR amplification. Six (37.5%) out of 16 patients died within the follow-up period. Four (66.7%) out of 6 patients who died had H3K27M mutation. Although the death rate of patients with H3K27 mutant tumors appears to be higher, this relationship did not reach statistical significance. The age and sex of the patients did not influence the location of the tumor or the H3K27M mutation status. Fourteen patients received radiation treatment to the tumoral region, 2 patients with H3K27M mutation received craniospinal irradiation since they already had spinal seedings at the time of diagnosis. All patients received temozolomide. Five out of 11 patients with H3K27M mutation enrolled in an OCN201 clinical trial. One patient who was also enrolled in an OCN201 trial died during follow-up. One patient who harbored both H3K27M and BRAFV600E point mutations received temozolomide and vemurafenib treatment. He is still alive without disease progression for 22 months. Patient demographics, presenting symptoms, interventions, pathological results, mutational status, and follow-up data are summarized in Table I.

DISCUSSION

Deep seated midline gliomas originating from the brainstem constitute 10% of all primary brain tumors in the pediatric age group (16). The incidence of pediatric gliomas originating from the thalamus ranges between 1%–5% (2). Several authors have proposed different classification systems for brainstem gliomas (9,10,23). They have been classified as diffuse intrinsic tumors, focal intrinsic tumors, dorsal or lateral exophytic tumors and cervico-medullary junction tumors according to their growth pattern and localization by Choux et al. (5). Focal tumors with homogeneous contrast enhancement are amenable to surgery and have a favorable prognosis (11). However, tumors with diffuse growth patterns on T2 weighted MRI are not surgically resectable. The prognosis is dismal and patients generally present with headache, nausea, vomiting, double vision secondary to ophthalmoplegia, motor deficits and disequilibrium (25,35). Thalamic gliomas were divided into three different groups as follows: unilateral thalamic gliomas, bilateral thalamic gliomas and thalamopedincular gliomas by Puget et al. (28). Although low grade thalamic tumors such as pilocytic astrocytomas can be removed surgically, high grade thalamic gliomas with a diffuse growth pattern are not amenable to surgery. Patients with these tumors present with motor or sensory deficits, psychological symptoms, hydrocephalus and, rarely, seizures (24). In our series, the patients' presenting symptoms were headache, disequilibrium, ophthalmoplegia, dizziness, panic attack and absence seizures (16). Since sur-

Table I: Patient Demographics, Presenting Symptoms, Interventions, Pathological Results, Mutational Status and Follow-Up Data

Case	Age (yrs)/ Sex	Symptom	Location	Intervention	Initial Pathology	Ki67 (%)	Molecular Alterations	Chemotherapy	RT	Outcome	Follow-up (months)
1	8.7/F	H/A	Unilateral Thalamus	OpenBx	Lowgrade	9	H3	VCR, Cyclophosphamide, CCNU, Temozolomide.	+	Alive	17.5
2	4.7/F	DysEq.	Pons	STX	Lowgrade	7	H3, ATRX	Temozolomide, ONC201	+	Alive	2.6
3	9.4/M	H/A, DysEq.	Bithalamic	EndoBx	Highgrade	10	H3	VCR, Limustine, CCNU, Temozolomide	+	Alive	20
4	14/M	Dizziness	Bithalamic	STX	Highgrade	30	H3, ATRX	Temozolomide, ONC201	+	Alive	1.5
5	12/M	Absence seizure	Unilateral Thalamus	STX	Lowgrade	2	No	Temozolamide	+	Alive	12,3
6	5.3/M	H/A, DysEq.	Brachium pontis / cerebellar hemisphere	Excision	Highgrade	90	H3	Cisplatine, VCR, Ifosfamide, Etoposide	+	Died	8
7	5.2/M	Ophthalmoplegia	Pons	STX	Lowgrade	5	H3, BRAFV600E	Vemurafenib, CCNU, Temozolamide, ONC201	+	Alive	22
8	5/F	DysEq., Ophthalmoplegia	Bitalamic	STX	Highgrade	25	ATRX	Temozolomide, Bevacizumab	+	Alive	33.3
9	6.4/M	Ophthalmoplegia	Pons	STX	Lowgrade	22	No	Temozolomide	+	Died	14.5
10	10/M	Ophthalmoplegia	Pons	STX	Lowgrade	10	H3	Temozolomide	+	Died	28.5
11	7.3/F	Ophthalmoplegia	Medulla oblongata	Excision	Highgrade	27	H3, PTEN, PDGFRA, EGFR	Temozolomide, Nimotuzumab, Dasatinib	+	Died	19.5
12	11/F	Panic attack	Unilateral Thalamus	Excision	Lowgrade	8	H3	Cisplatin, VCR, Ifosfamide, Etoposide, ONC201	+	Died	35
13	5.8/M	H/A	Unilateral Thalamus	OpenBx	Highgrade	20	H3	Temozolomide	+	Alive	27.5
14	8/F	H/A, DysEq.	Unilateral Thalamus	OpenBx	Highgrade	80	ATRX, PTEN, EGFR	Cisplatin, Ifosfamide,	+	Died	16
15	9.2/M	DysEq.	Medulla oblongata	Excision	Lowgrade	3	ATRX	Carpoplatin	+	Alive	25.5
16	5/F	Ophthalmoplegia	Pons	STX	Highgrade	12	H3	Temozolamide, ONC201	+	Alive	3

CCNU: *Lomustine;* ***DysEq.:*** *Disequilibrium;* ***EndoBx:*** *Endoscopic biopsy;* ***H/A:*** *Headache;* ***OpenBx:*** *Open biopsy;* ***RT:*** *Radiation treatment;* ***STX:*** *Stereotactic biopsy;* ***VCR:*** *Vincristine.*

gery is not indicated for diffuse brain stem tumors and routine histopathological diagnosis did not change patients' treatment options, biopsy for diffuse brainstem tumors was abandoned until recent years (1). Following advances in gene sequencing techniques, when Sanger sequencing became readily available, researcher's began to sequence central nervous system (CNS) tumors in order to investigate the molecular basis of the disease (22). This led to the observation that methylation analysis of CNS tumors assists in the identification of the molecular fingerprints of different CNS tumors (12). Sturm et al. reclassified CNS primitive neuroectodermal tumors (PNETs) according to their methylation profiling. They discovered that tumors previously classified as PNETs share common fingerprints with well-known CNS tumors such as high grade gliomas, medulloblastomas, ependymomas, Ewing's sarcomas, embryonal tumors with multilayered rosettes, atypical teratoid rhabdoid tumors (AT/RTs), meningiomas, and so forth. They also discovered new molecular CNS tumoral pathologies (34). Their study practically discarded the CNS histopathological term"PNET" from classification guidelines. The other question raised as a consequence of these molecular advancements was "can CNS tumors be treated by specific medications that target disease-causing mutations?" Several studies subsequently drew attention to the prognostic and therapeutic impact of molecular alterations such as IDH1/2, H3K27M, H3G34R, BRAFV600E, mTOR mutations, MGMT methylation, EGFR, PDGFRA amplification and PTEN loss in pediatric glioma patients (6,14,21,29,30,38). The WHO adopted the molecular alterations of CNS tumors into their CNS pathological diagnosis guidelines and advised pathologists to establish their diagnoses using a combination of morphological and molecular diagnostic methods (18). In the WHO 2016 CNS tumor classification system, brainstem gliomas are contained within midline gliomas, which include thalamic gliomas. In this system, midline gliomas are also divided into two groups according to the presence or absence of H3K27M mutation. Tumors with H3K27M mutations are named diffuse midline gliomas (DMGs) and their biological behavior is similar to that of grade 4 tumors regardless of their grade on histological diagnosis (18). In our series, the pathology result of 5 tumors that were previously diagnosed as grade 2 diffuse astrocytomas, were revised as DMGs (grade 4) following confirmation of H3K27M mutation. H3K27M mutation is formed by the substitution of lysine amino acid for methionine amino acid at the 27th position in histone H3 (either histone 3.1 or 3.3 genes). This mutation has effects on chromosome remodeling and epigenetic activation or inhibition of different elements of the genome (13). H3K27M mutation is the most common mutation in midline gliomas and H3K27M mutant tumors have worse prognosis than H3K27M wild type ones (21). H3K27M mutation prevalence is 75% in diffuse pontine gliomas and 50% in thalamic, medullary and spinal cord gliomas (33). Its prevalence in our series was 80% for diffuse pontine gliomas, 62% for diffuse thalamic gliomas and 50% for medulla oblongata tumors. After the integration of tumor molecular data into the WHO 2016 classification system for CNS tumors, our department started to conduct molecular investigations routinely during pathological diagnosis and to use the findings to tailor the treatment of pediatric CNS tumors. Our first molecular tests consisted of IDH1/2, H3K37M/G34R, ATRX/TERT, and BRAFV600E mutations, PDGFRA and EGFR amplifications, and PTEN loss. Recently we have designed a new, custom made brain tumor molecular panel with the department of pathology. It allows the user to test tiny tumor particles for more than 80 different molecular alterations previously described within CNS tumors. Our department policy for midline tumors is to resect all pathology that is surgically excisable, such as focal low grade midline gliomas, and send samples for morphological and molecular pathology. Our policy for surgically unresectable midline tumors such as diffuse thalamic, pontine, and medulla oblongata gliomas is to obtain a biopsy through either stereotactic methods or craniotomy, for morpho-molecular integrated diagnosis and tailoring of adjuvant treatments.

Although biopsy for diffuse midline tumors such as diffuse pontine gliomas was not indicated within previous decades, emerging studies recommend stereotactic biopsy of these tumors for more accurate diagnosis and treatment (17,27). Puget et al. reviewed the literature on brainstem stereotactic biopsies in 892 pediatric and adult patients, including their own pediatric series with 130 children, and reported that the diagnostic yield was 96%, transient morbidity was less than 4%, permanent morbidity was less than 1% and mortality was less than 0.5% (27). Samadani and Judy conducted a meta-analysis of 13 studies with 381 adult and pediatric patients who had undergone a stereotactic brainstem biopsy. They concluded that 96% of biopsies were diagnostic with 1% permanent morbidity, 4% temporary morbidity and 0.3% mortality (32). Another meta-analysis by Pincus et al. including192 children who underwent a brainstem biopsy reported that 95% of procedures were diagnostic with 5% morbidity and 0.7% mortality (26). There are also studies in the literature reporting higher rates of mortality of stereotactic brainstem biopsies (7,37). Dellaretti et al. reported their case series of 44 pediatric patients who had undergone brainstem stereotactic biopsies. They concluded that 93.1% of the biopsies were diagnostic with 9% morbidity (7). Wang et al. studied 15 pediatric patients who had undergone stereotactic brain biopsy. They reported that all biopsies were diagnostic with 20% morbidity and without any mortality (37). The sampling strategies for diffuse thalamic lesions may vary according to the location of the tumors. Tissue samples from bithalamic tumors may be obtained by stereotactic or open biopsy, and from unilateral diffuse thalamic tumors by stereotactic biopsy, open biopsy or excisional biopsy (2,8,24,28). Bilginer et al. studied 37 unilateral and 8 bithalamic pediatric tumors with a focal or diffuse growth pattern. They operated on 33 out of 37 unilateral thalamic tumors (6 partial resection, 21 subtotal resection, and 6 total resection). They obtained tissue samples through open biopsy in 4 out of 8 bithalamic tumors. They reported no permanent morbidity and no perioperative mortality (2). Puget et al. reported their series of pediatric thalamic tumors including ones with both a focal and diffuse growth pattern. The total number of unilateral thalamic tumors was 54. Seventeen of them were biopsied (biopsy method was not specified), 32 of them had an excisional biopsy (5 had total excision, 27 had partial or subtotal excision) and 5 of them

had no surgery. Regardless of the method in which the biopsy was obtained, they reported 32% perioperative morbidity and 4% perioperative mortality (28). Another study by Ozek and Ture including 18 pediatric patients with unilateral thalamic tumors, reported gross total resection in 16 patients with no perioperative mortality. The study did not report on morbidity (24). Di Rocco and Iannelli described 4 pediatric patients with bithalamic tumors. They performed stereotactic biopsy in 3 patients and a partial excision in 1 patient. There was no morbidity and no report on mortality (8). There appears to be no consensus regarding the method of obtaining tissue samples from diffuse thalamic tumors in the literature. However, there is a tendency to obtain biopsies of unilateral thalamic tumors through excisional or open biopsy and to obtain biopsies of bithalamic tumors through the stereotactic route. In our current series we obtained tissue samples through stereotactic biopsy in 8 patients. Five patients had a pontine tumor, one patient had a unilateral thalamic tumor and 2 patients had bithalamic tumors. We obtained tissue samples through open biopsy in 3 unilateral thalamic tumors, through excision in 1 unilateral thalamic tumor, 2 medulla oblongata tumors and one brachium pontis tumor, and through endoscopic biopsy in 1 bithalamic tumor. There was no morbidity or mortality related to these interventions. The median overall survival of patients with DMG ranged between 8 and12 months with standard RT and Chx (20). Although thus far there is no effective therapy for the treatment of DMGs, families and researcher's try to find new strategies to improve patient prognosis. Taking a biopsy of diffuse midline tumors using the stereotactic method and obtaining a tumor sample for molecular testing gives patients a chance to try targeted therapy regimens or enter clinical trials. There are some anecdotal reports of BRAFV600E mutated pediatric glioblastoma and pleomorphic xanthoastrocytoma cases which responded to vemurafenib, which specifically inhibits the product of this mutation (3,31). In our series, one patient (case 7) with BRAFV600E point mutation whose tumor sample also exhibited H3K27M mutation received RT and Chx with temozolomide, CCNU. He is clinically and radiologically progression free for more than 22 months. Since our follow-up time is 18 months and ranges between 1.5 and 35.2 months we have no exact results regarding survival rates in the cohort as yet.

There are studies investigating the treatment of PDGFRA amplified DMGs using inhibitors of tyrosine kinase receptors which inhibit the PDGFR signal pathway, such as dasatinib. There are also studies investigating the treatment of DMGs with PTEN loss using everolimus, sirolimus/rapamycine (19). In our series, the tumors in case 11 and 14 showed PTEN loss. Case 11 received RT and Chx with Cisplatin and Ifosfamide. She was in remission under these regimens but progressed rapidly after the 14th month of follow-up, could not receive mTOR inhibitors and died within 16 months.

The tumor in case 11 had PDGFRA and EGFR amplification and also PTEN loss. She had RT and Chx with Temozolomide, Nimotuzumab, and Dasatinib. She was alive for 19 months. She could not receive mTOR pathway (PTEN loss) inhibitors such as sirolimus/rapamycine because of a low Karnofsky performance score.

There is also another clinical trial called the ONC201 trial. ONC 201 is a selective inhibitor of dopamine receptor DRD2/3. DRD2/3 receptor facilitates tumor growth in gliomas. ONC201 antagonizes the signals of DRD2/3 receptor and causes tumor regression (4). There is a report of a 22-year-old woman with a H3K27M mutant thalamic tumor treated with ONC 201. The tumor regressed by more than 95% of its size at the time of diagnosis. According to data obtained from preclinical studies and anecdotal case reports, it is supposed that H3K27M mutant gliomas show increased sensitivity to ONC201 (4). The inclusion criteria for this trial are a diagnosis of H3K27M mutant glioma and prior RT. This trial started in August 2018 (4). The result of this trial is still pending, however clinicians are hopeful for better outcomes for patients, with longer progression free survivals. Five out of 11 eligible patients have been included in the ONC201 trial from our series. The other 6 patients did not receive treatment because some of them died before the trial started or could not support travel and treatment expenses.

CONCLUSION

Midline gliomas with a diffuse growth pattern are rapidly progressive brain tumors with a dismal prognosis which are more commonly encountered in the pediatric population. Tissue samples from these tumors are essential for determining patients' morphomolecular diagnoses, targeted treatment strategies, and/or their eligibility for clinical trials. Tissue samples may be obtained either by stereotactic biopsy, open biopsy or excisional biopsy (partial excision-especially in expansile thalamic tumors or exophytic diffuse brainstem tumors) with acceptable morbidity and very low mortality. The method of obtaining tissue samples should be tailored according to the localization of the tumor and the experience of the neurosurgeon.

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