Treating Hydrocephalus in Midline Gliomas with an H3 K27M Mutation

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Background: Diffuse midline gliomas (DMG) are a subset of malignant gliomas that share a characteristic Histone H3K27M mutation. These tumors are centrally located and may cause hydrocephalus on initial presentation. DMG lack characteristic imaging that distinguish from other primary brain tumors in the midline. We conducted this retrospective chart review of 43 consecutive patients presenting with midline tumors to determine: how many had a DMG ; whether DMG patients with hydrocephalus were candidates for resection; and what the outcomes of endoscopic third ventriculostomy (ETV) versus ventriculoperitoneal shunt (VPS) placement were, as compared to wild type (WT) tumors.

Methods: An IRB approved retrospective chart review of patients was done from 9/2016 to 3/2020. In total 43 patients, a mix of adult and pediatric patients, with midline glioma tumors were analyzed. Data was collected to determine the ages, the neurosurgical interventions, whether the patient had the H3K27 mutation, hydrocephalus, and the overall survival. Chi-square analyses and t-tests were done to calculate significance between clinical groups. Kaplan Meier curves were used for time to event analysis with log-rank testing for significance.

Characteristic	WT	H3K27M	P-Value
Age (Std. Deviation)	16.3 +/- 26.6	23.4 +/- 14.7	0.3
Gender			0.665
Male	21	8	
Female	11	3	
Hydrocephalus			0.00098
Yes	6	8	
No	26	3	
Initial Diversion			0.0047
ETV	1	4	
VPS	0	4	
Resection	5	0	

Table 1. Clinical Characteristics of Patients Who Presented with Midline Primary Brain Tumors. There was no difference in age nor gender between patients with WT or H3K27M gliomas. There was a significant difference in the hydrocephalus and the initial diversion of the wild type vs the H3K27M patients. Abbreviations as follows: WT = wildtype, H3K27M = Histone 3 gene K27M mutation, ETV = Endoscopic Third Ventriculostomy, and VPS = ventriculoperitoneal shunt.

Figure 1

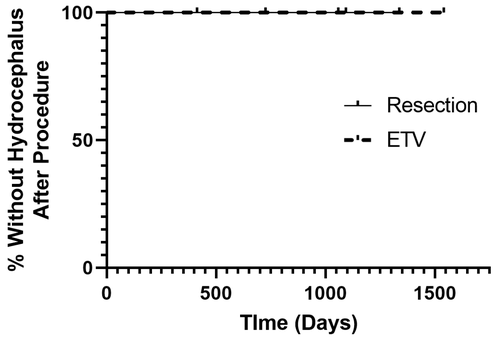

Figure 1. Kaplan Meier curve of the wild type glioma patients demonstrating the time to event analysis of freedom from hydrocephalus. None of these wild type patients had recurrent hydrocephalus after initial ETV or resection. None of these patients underwent VPS.

Figure 2

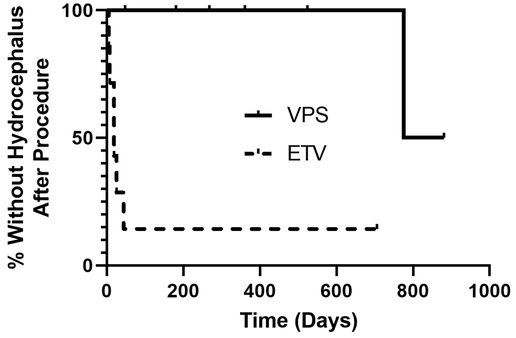

Figure 2. Kaplan Meier of the H3K27M patients time to event analysis of freedom from hydrocephalus. In all of the H3K27M patients who underwent ETV to treat their hydrocephalus, all of their ETVs had failed. In comparison to the H3K27M patients who had VPS, all of the patients were successful in controlling their hydrocephalus except for one failure, with an odds ratio of 43.6 for treating hydrocephalus favoring VPS over ETV (95% CI 5.3-362.2)

Figure 3

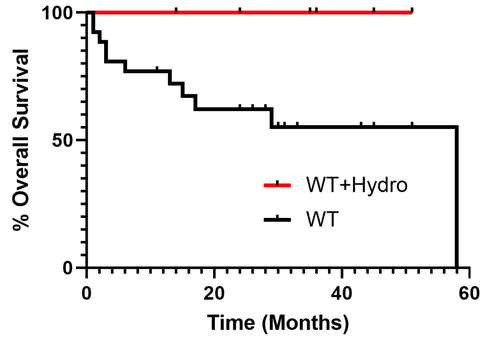

Figure 3. Kaplan Meier of WT patients time to event analysis of overall survival. WT glioma patients with hydrocephalus (n=6) did not reach median survival while WT glioma patients without hydrocephalus (n=26) had a median survival of 58 months, P =0.07.

Figure 4

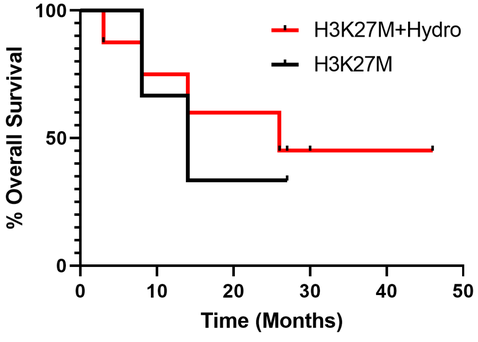

Figure 4. Kaplan Meier of H3K27M patients time to event analysis of overall survival. H3K27M glioma patients with hydrocephalus (n=8) similar median survival compared to H3K27M glioma patients without hydrocephalus (n=3), P =0.73 with 14 months versus 26 months.

Results: The median age of all midline tumor patients was 19.1 years (range 1.1-80.1). 26% (11/43) of midline tumors presented with H3K27M mutation, with a higher rate of hydrocephalus compared to patients without mutation [7/11 (65%) for DMG vs. 6/32 (19%) for WT, $p<0.05$]. Of the seven H3K27M patients presenting with hydrocephalus, none were candidates for resection, 5 underwent ETV, and 2 underwent VPS placement as initial management. 4 out of these 5 ETVs failed within an average of 24 days (6-42 days). 2 patients then underwent VP shunt placement; the other 2 underwent secondary ETV but both failed and required VP shunting as well. All 6 WT tumor patients had one procedure (1 ETV, 5 resection) to relieve hydrocephalus, and no patients had recurrent hydrocephalus.

Conclusions: The initial presentation of midline primary brain tumors in both pediatric and adult patients involves evaluation for hydrocephalus. Patients with hydrocephalus and non-resectable tumors are more likely to harbor H3 K27M mutations which are associated with worse overall survival. Resectable tumors are more likely to have WT H3 loci. Patients with hydrocephalus do not have worse overall survival regardless of underlying WT versus H3K27M. However, these data suggest that neuroendoscopic third ventriculostomy and septum pellucidum fenestration for the management of obstructive hydrocephalus in patients with H3K27M may be less robust than shunting. As H3K27M analysis is not available rapidly at initial presenation, interdisciplinary neurosurgery, neuro-oncology, and radiation oncology is warranted to coordinate patient care.