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Hetero- and homozygous germline mutations of the mismatch repair genes MLH1, PMS2, MSH2 and MSH6 cause Lynch and constitutional mismatch repair (CMMRD) cancer predisposition syndrome, respectively. Affected CMMRD individuals are at risk to develop a variety of neoplasms including CNS tumors, particularly high grade gliomas (HGG), during childhood. Currently, few data exist on the prevalence of CMMRD in children with pediatric HGG. We screened a consecutive series of 79 supratentorial HGGs. Tumor tissue was available in 42 patients, 5 were reclassified as non-HGGs. Immunohistochemistry with antibodies against MLH1, PMS2, MSH2 and MSH6 was performed in 37 tumors. Four patients (3 families) with known CMMRD were included. The evaluation of the slides was performed blinded to the CMMRD status. All four patients with known CMMRD (3 patients with PMS2, one with MSH6 mutation) were identified, showing loss of PMS2 and MSH2/MSH6, respectively. Additionally, we identified 6 patients with loss of MSH2/MSH6 staining in tumor cells, but retained staining in preexisting cells, indicating a pattern like in Lynch syndrome. NGS sequencing of these tumor tissues revealed in 2 patients *MSH2* mutations and in one patient a hypermutator phenotype with *MSH2* and *MSH6* mutations. In 3/6 patients no mutations in the MMR genes were detectable. In summary, we found a low prevalence of CMMRD among HGGs, but identified also 2 patients with probable Lynch syndrome. Immunhistochemistry is an effective tool to screen for patients with MMR defects and should be performed in HGGs to optimize treatment and offer affected families genetic counseling.

HGG-45. PROTEOMIC ANALYSIS OF PEDIATRIC DIFFUSE ASTROCYTOMAS YIELDS PATHWAYS ASSOCIATED WITH BOTH PROGRESSION-FREE AND OVERALL SURVIVAL

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Brain tumors are now responsible for more deaths each year than any other childhood cancer. Current studies aim to discover key molecular drivers that can explain prognosis and serve as targets for new therapeutic approaches, reducing morbidity. In this study, we performed LC-MS/MS proteomics on a cohort of 28 primary diffuse astrocytoma formalin-fixed paraffin embedded samples (WHO Grades II-IV) from patients at Nationwide Children's Hospital with a median follow-up time of 2.3 (0.6–20.2) years. Ingenuity Pathway Analysis was used to analyze the proteomic data after using both age and grade as covariates and only including proteins with p-values less than 0.05. The upregulation of a well-known oncogenic pathway, the Protein Kinase A signaling pathway, was significantly associated with greater risk of progression and death (P=5.5E-07 and P=4.6E-04). Integrin signaling, a pathway commonly suppressed in cancer, was similarly downregulated in those with greater risk of progression and death (P=3.3E-04 and P=1.7E-07). A global upstream analysis of the proteomic data also predicted activation of the oncogene MYCN in those who performed poorly, supporting previous studies. When comparing grade II (n=10) to grade III (n=8) and IV (n=10) primary tumors, the pathway most upregulated in higher histopathological grades was EIF2 Signaling (P=4.9E-49). This pathway has previously been associated with resistance in adult glioblastoma. These pathways, and the proteins detected within, may provide novel means by which to better understand and treat pediatric diffuse gliomas. Ongoing studies are in progress to understand how these pathways drive aggressiveness and differ from adult astrocytomas.

HGG-47. DECREASED GROWTH VELOCITY WITH LONG TERM USE OF BRAFV600E AND MEK INHIBITION IN A PATIENT WITH ANAPLASTIC GANGLIOGLIOMA

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PURPOSE: To describe decreased growth velocity with long term use of BRAFV600e and MEK inhibition in a patient with anaplastic ganglioglioma. RESULTS: 4-year-old patient was found to have a 6 x 4.6 x 5 cm mass in the hypothalamus. Pathology consistent with anaplastic ganglioglioma and chromosomal microarray revealed a BRAFV600e mutation. Patient started on dabrafenib and trametinib and tumor decreased 85% after 3 months. She is stable without significant toxicities 39 months on therapy, and is now 8 years old. Patient had been growing at the 25% for weight and 12% for height but is now 65% for weight and 0.5% for height. It is difficult to tease out the relationship between the tumor, the location of the tumor, and the BRAF and MEK inhibitors and their effect on growth. Discussions with the family and endocrinology are ongoing but being <1% for height will lead to decrease in quality of life. CONCLUSIONS: Further follow-up study is needed to determine if this is truly a long-term toxicity, or if this may just be a direct result of the location of the tumor. Would supplementation with growth hormone in this patient lead to losing control of a high grade tumor, or would it simply replace a hormone that is not produced?

HGG-48. ROS1 INHIBITOR ENTRECTINIB USE IN RELAPSE/ REFRACTORY INFANTILE GLIOBLASTOMA WITH POSITIVE ROS1 FUSION - A CASE REPORT WITH PROMISING RESPONSE

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INTRODUCTION: Infantile glioblastoma is rare with poor prognosis. Recent molecular study for infantile hemispheric high grade glioma found its association with ALK/ROS1/NTRK/MET pathway. This suggested the potential use of targeted therapy for refractory / relapse patients. CASE: A newborn presented with apnea, CT brain showed intracranial haemorrhage. MRI then showed a left parietal tumour with bleeding and mass effect. Craniotomy achieved subtotal resection. Chemotherapy VCR/CPM alternating with CDDP/VP-16 was given for one year. Patient was stable with static residual tumour during chemotherapy. However patient developed status epilepticus two weeks after off treatment. MRI showed significant tumour progression which required 2nd & 3rd debulking surgery. Molecular assay by nanostring panel showed BRAF-KIAA1549 fusion. MEK inhibitor Trametinib was tried for 3 months and stopped as disease progression. Further molecular assay by RNASeq showed presence of ROS1 fusion (ZCCHC8-ROS1) while absent of BRAF fusion. Patient underwent 4th debulking surgery as impending herniation while waiting for the targeted therapy. It was complicated with right hemiplegia and facial nerve palsy postoperatively. Finally, ROS1 inhibitor Entrectinib was started 2 weeks later. It was well tolerated without significant adverse reaction. Patient made dramatic neurological recovery including improved facial nerve palsy, able to walk unaided and self feed. MRI brain 1 and 3 months after Entrectinib showed interval reduction in residual tumour. Patient is currently progression-free for 6 months. CONCLUSION: Early molecular study for infantile glioblastoma is useful to guide novel therapy. Molecular result may varies between different panels or change over time, to be interpreted with caution.

HGG-49. A PEDIATRIC THALAMIC HIGH-GRADE GLIOMA WITH *H3F3A* K27M AND *BRAF* V600E DOUBLE MUTATIONS

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CASE: A 18-month-old boy presented with approximately 2 months history of progressive left hemiparesis and left exotropia. MRI study showed a 3–4 cm T1-iso, T2-high tumor at right thalamus to midbrain with little contrast enhancement. The patient underwent endoscopic biopsy of the tumor, which showed relatively dense proliferation of small cells with round nuclei, mitosis of the tumor cell, but no necrosis. Immunohistochemical showed positive stain of GFAP and Olig2. Ki-67 was 34%. The histopathological diagnosis was compatible with high grade glioma. Chemotherapy with vincristine, cyclophosphamide, cisplatin and etoposide was initiated. Molecular testing of the tumor revealed *H3F3A* K27M and *BRAF* V600E double mutations in DNA from frozen tumor tissue. DISCUSSION: The concurrent mutation of *H3F3A* K27M and *BRAF* V600E in pediatric glioma is very rare, but there are several cases previously reported in literature. Interestingly those cases are heterogenous in age, location, histopathological subtypes and clinical outcome.