were extracted from subjects registered in the International DIPG registry (IDIPGR). Univariable analyses was performed using the Fisher's exact test or Wilcoxon rank sum test. Survival was estimated using the Kaplan-Meier method. RESULTS: Evaluable patients (n=542) met criteria for DIPG diagnosis by central radiologic review; of those, 126 (23%) had permanent CSF diversion. Median time from diagnosis to diversion was 0.5 months (IQR 0.1-4.5 months). Those with permanent diversion were significantly younger (median 5.4 years vs 7.0 years, p<0.001) and had higher incidence of hydrocephalus at diagnosis (65.3% vs 11.9%, p<0.001). Permanent CSF diversion did not significantly impact overall survival (OS) (p=0.4), even amongst the 124 patients with hydrocephalus at presentation (p=0.20). Those with permanent diversion prior to radiation therapy demonstrated longer median OS than those in whom diversion was placed after radiation (14.3 vs 9.6 months, p=0.001). Patients reported significantly less headache and vomiting at last follow up after permanent CSF diversion compared to pre-diversion (p<0.0001 and p=0.001, respectively), however steroid use was also significantly higher at last follow-up after CSF diversion (p<0.001). CONCLUSIONS: Amongst an international cohort, DIPG patients who had permanent CSF diversion were significantly younger and had higher rates of hydrocephalus at initial presentation than those without permanent diversion. Symptoms of increased intracranial pressure improved in those with CSF diversion, although a direct effect may be confounded by increased steroid use. Permanent CSF diversion did not prolong overall survival in this large cohort of patients, even amongst those who presented with hydrocephalus.

DIPG-26. TARGETED PROTEIN DEGRADATION OF LSD1 SYNERGIZES WITH HDAC INHIBITORS IN DIFFUSE INTRINSIC PONTINE GLIOMA

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Diffuse intrinsic pontine glioma (DIPG) remains one of the most lethal brain tumors in all of childhood with no effective treatments besides radiation, which only extends survival a few months. Against this backdrop, our lab recently executed a focused CRISPR negative selection screen in DIPG cell lines after treatment with the histone deacetylase (HDAC) inhibitor panobinostat and discovered a strong co-dependence with the histone demethylase LSD1. To further explore the therapeutic potential of this synergistic interaction, we tested a drug library of HDAC- and LSD1- targeting drugs with the goal of identifying a combination with optimal synergy and blood brain barrier (BBB) penetration suitable for clinical translation. We were surprised to find that traditional catalytic LSD1 inhibitors had minimal effect in isolation and did not seem to synergize with HDAC inhibitors, while a recently described CoREST/LSD1 degrader named UM171 phenocopied the effects seen in our CRISPR screen. Degraders are a class of compounds that recruit an E3 ubiquitin ligase to a protein-of-interest and cause target ubiquitination and proteasomal degradation. Given our unexpected finding, we hypothesized that UM171 induces synergy with HDAC inhibitors through elimination of a scaffolding function of LSD1. To prove this, we knocked out LSD1 using CRISPR/Cas9 and subsequently treated with a panel of HDAC inhibitors, which showed a signification sensitization of DIPG cells to HDAC inhibitors compared to standard controls. We also confirmed that UM171 interacts with the CoREST complex (members include LSD1, RCOR1, HDAC1/2) by performing streptavidin bead pull down with a newly synthesized biotin-conjugated UM171 probe. In summary, our results show that targeting LSD1 for degradation in combination with HDAC inhibition is a synergistic strategy in DIPG worthy of further translational study.

DIPG-27. BEHAVIORAL DISTURBANCES AS UNDERESTIMATED PRESENTING SYMPTOMS IN CHILDREN WITH DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

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PURPOSE: to describe how often behavioral and emotional changes occur at diagnosis in children with DIPG, or precede it. METHODS: the anamnesis, clinical history, psychological evaluation, and onset symptoms of all cases of DIPG diagnosed at Gaslini Institute between January 2010 and December 2020 were reviewed. RESULTS: 20 DIPGs were diagnosed, 7 males, with a median age of 7,6 years (range 2,4-16,2). All patients presented typical neurological symptoms: 16 had cranial nerves palsy, 12 ataxia, 8 dysarthria, 5 dysphagia, 5 hemiparesis, 5 headache, and 2 obstructive hydrocephalus. Behavioral disorders were found in 14 cases, with several manifestations and in various association: irritability and aggressive behavior in 6, ideomotor slowdown and apathy in 5, emotional dysregulation in 4, mood deflection in 3, sleep disturbances (*i.e.* nightmares, insomnia, and somniloquy) in 3, marked behavioral changes, school phobia and separation anxiety in 2, depersonalization crisis and phobia of waterdrops in the eyes in 2 patients each. In 6 cases behavioral disturbances were the presenting symptom, appearing one to twelve months earlier than the classic neurological deficits. In all patients, behavioral symptoms improved during Radiotherapy. CONCLUSIONS: behavioral disturbances, although well-known and described in the literature, are not commonly reported among the onset symptoms of DIPG, thus being probably underestimated. Their pathogenesis can be explained by neurophysiology: the brainstem contains reciprocal cerebro-ponto-cerebellar connections whose disruption compromises their modulatory function on affective and cognitive behavior. Furthermore, the reticular formation contains aggregates of neurons regulating several complex functions including the state of alertness (*e.g.* sleep and wakefulness), the perception of pain, and cognitive functions (*e.g.* attention, mood, and memory). A careful anamnestic and medical history together with a detailed psychological assessment should be always performed in all DIPGs at diagnosis, in order to bring out those underlying behavioral disorders which could benefit from early neuropsycological support.

DIPG-28. INDOLENT *H3 K27M*-MUTANT DIFFUSE MIDLINE GLIOMA

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INTRODUCTION: *H3 K27M*-mutant diffuse midline glioma (DMG) is an aggressive central nervous system tumor that is universally fatal with a median survival of 8-12 months after diagnosis. Here we present a patient who was incidentally found to have a lesion within the right thalamus on brain magnetic resonance imaging (MRI). Twelve years later, she was found to have a brain mass within the same area with pathology consistent with an *H3 K27M*-mutant DMG. CASE DESCRIPTION: A 14-year-old female presented with new onset left-sided numbness and weakness, blurry vision and a right-sided temporal headache. Her past medical history is significant for severe persistent asthma and anoxic brain injury secondary to a cardiopulmonary arrest at 2-years-of-age due to an asthma exacerbation. She has had multiple MRIs of her brain since her initial insult which initially showed the presence of a T2/FLAIR hyper-intense lesion within the right medial thalamus in addition to chronic central nervous system changes. The right thalamic lesion was stable in size between images obtained at 2-years and 4-years of age. Her current physical exam is significant for decreased strength to her left upper and lower extremities. Brain MRI with and without contrast is obtained with partial effacement of the third ventricle due to mass effect from an enlarging mass from the right thalamus. Biopsy of the lesion demonstrated an *H3 K27M*-mutant DMG, WHO grade IV. Our patient went on to receive palliative radiation therapy with 59.4 Gy over 33 fractions. DISCUSSION: This case illustrates an unusual presentation of an *H3 K27M*-mutant DMG with an indolent course, diagnosed twelve years after the initial MRI finding. This proposes the possibility of multiple factors playing a role in the oncogenesis of these aggressive tumors and that further research is warranted.

DIPG-29. HIGHLY MULTIPLEXED DIGITAL SPATIAL PROFILING OF THE TUMOR IMMUNE ENVIRONMENT OF PEDIATRIC AND ADULT *H3 K27M*-MUTANT DIFFUSE MIDLINE GLIOMAS

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BACKGROUND: *H3 K27M*-mutant diffuse midline gliomas (DMGs) are highly aggressive malignancies of the central nervous system that affect both pediatric and adult populations. The immune layout and genetic changes within the tumor microenvironment associated with these high-grade malignancies are thought to play an integral role in the phenotypic differences in tumor presentation and clinical course between both populations. Comparative immune landscape between pediatric and adult DMGs is not known. METHODS: The NanoString GeoMx™ Digital Spatial Profiler platform was used to determine the immune marker and genetic layout in a cohort of both pediatric and adult *H3 K27M*-mutant DMG tissue samples. Three fluorescently labeled antibodies targeting immune cells (CD45), epithelial cells (PanCK), tumor cells (*H3 K27M*) and a nucleic acid stain (SYTO-13) were used to identify and separate out the various components within the tumor tissues from selected regions of interest. The resultant information was then pooled into libraries that were run through the Illumina sequencing system to assess gene expression and proteomics for both cohorts of samples.