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INTRODUCTION: Whilst most patients with PLGG will survive, varying morbidities derived from patient,tumour & treatment characteristics can afflict life-long disabling functional impairments. No PLGG studies have evaluated potential prognostic factors for important functional outcomes. METHODS: We performed retrospective analysis of all children diagnosed with PLGG at GOSH 1980-2021.Review of medical notes recorded patient demographics,tumour characteristics & treatment data.Functional outcomes included endocrine,educational,visual (in OPG),auditory & physical function.Multivariate regression analysis($p<0.05$) examined associations between biological prognostic variables & functional outcomes. RESULTS: 814 patients were diagnosed with PLGG.731(90%) had 5-years follow-up from diagnosis & were included for functional analysis.Median age at diagnosis 7 years(0-17.9); 50.6%Male,12.2% NF1.Tumours were cerebral(27%),cerebellar(27%),hypothalamo-chiasmatic(19%),brainstem(7%),or other(20%);with disseminated disease in 5%.Pilocytic Astrocytoma constituted 46%.Molecular profiling of 133 revealed *5%BRAFV600E mutation*,42%*BRAF-KIAA1549* fusion.Treatments included: Surgery(70%),Chemotherapy(20%),& Radiotherapy(21%).20-year-OS 94%,PFS 76%;median follow-up 16 years(5-38). Documented neurocognitive deficiency(30%) associated with chemotherapy(HR2.36,95%CI 1.49-3.75,P<0.001), radiotherapy(HR 2.25,95%CI1.5-3.36,P<0.001) & male gender(HR 0.68,95%CI 0.49-0.95,P0.02)as independent poor-prognostic risk-factors.Chemotherapy(HR 5.7,95%CI1.4-22.3,P0.01) & radiotherapy(HR6.77,95%CI2.1-22.0,P0.001) were independent risk-factors for requirement of Educational-Health-Care-Plans(25%).9% attended specialised schools. Combined-limb-MRC-grade <18/20(6.4%) was independently-associated with receiving chemotherapy(HR 2.77,95%CI1.29-5.93,P0.01),& radiotherapy(HR 6.28,95%CI3.25-12.15,P<0.001).6% mobilised by wheelchair.Resolution of seizures occurred in 68% of 176 following PLGG treatment. Single/multiple endocrinopathies occurred in 9.3%/11%.Presence of 2+Endocrinopathies was associated with chemotherapy(HR6.82,95%CI4.0-14.4,P<0.001), radiotherapy(HR7.81,95%CI4.3-14.3,P<0.001),NF1(HR2.9,95%CI1.3-6,P0.01),OPGs(HR 1.3,95%CI1.2-1.5,P<0.001);with younger diagnostic-age(HR0.80,95%CI0.74-0.87,P<0.001) & initial surgical resection(HR0.3,95%CI0.15-0.7,P0.03) independent protective factors. Receiving chemotherapy/radiotherapy were independent prognostic-factors for Post-PLGG-treatment Brock grade 1+ hearing impairments(2.2%).Visual outcomes in 146 OPG patients:blindness in atleast 1 eye(4.8%),registered visual impairment(9.6%),& visual-aid use(6.2%). **CONCLUSIONS**: Whilst overall outcomes for PLGG are optimistic, some patients have significant functional impairments detrimental to quality-of-life.Further evaluation of longer-term functional outcomes and prognostic associations is justified.

LGG-47. SINGLE-CELL RNA SEQUENCING REVEALS IMMUNOSUPPRESSIVE MYELOID CELL DIVERSITY DURING MALIGNANT PROGRESSION IN GLIOMA

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Myeloid cells and macrophages have been shown to promote immunosuppression in high-grade gliomas (HGG), however their roles in malignant progression of low-grade glioma (LGG) are poorly understood. Here, we investigated the heterogeneity of the immune microenvironment during glioma progression using a murine model that recapitulates the malignant progression of low to high-grade glioma. To that end, we performed single-cell RNA sequencing on CD45+ immune cells isolated from animals bearing no tumor (NT), LGG, and HGG. We observed an increased infiltration of CD4+ T cells, CD8+ T cells, B cells, and natural killer cells in the tumor microenvironment of LGG, whereas this infiltration was abrogated in HGG. Our study identified two distinct macrophage clusters across all 3 samples, with signatures of bone marrow derived and resident macrophages, respectively. These macrophages showed an immune-activated phenotype *(Stat1, Tnf, Cxcl9 and Cxcl10)* in LGG, but then evolved to a more immunosuppressive state (*Lgals3, Apoc1 and Id2*) in HGG, restricting T cell recruitment and activation. In addition, we identified CD74 and macrophage migration inhibition factor (MIF) as potential targets for both these distinct macrophage populations, based on their increased expression in LGG and HGG compared to NT. Targeting these factors during the LGG therapeutic window may inhibit myeloid cells and intra-tumoral macrophages and attenuate their immunosuppressive properties and impair malignant progression.

LGG-48. THE INFLUENCE OF DIFFERENT FGFR1 ALTERATIONS ON PEDIATRIC LOW-GRADE GLIOMA TUMOR BIOLOGY AND TARGETED THERAPY RESPONSE

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Pediatric low-grade gliomas (pLGGs) have excellent survival, however, with current standard of care, most patients suffer lifelong severe sequalae. pLGGs are almost exclusively driven by single activating mutations in the MAPK pathway. Clinical trials with small molecule inhibitors in BRAF-altered pLGGs are showing promising results in early clinical trials, and similar efforts are now underway for FGFR1-altered tumors, however the underlying biology and treatment response has not been thoroughly explored in a pre-clinical setting. To explore the genetic landscape of FGFR altered gliomas we assembled a cohort of 87 patients with FGFR1-4 altered gliomas across Dana-Farber Cancer Institute, Boston Children's Hospital and Brigham and Women's Hospital. Within this cohort we observed that pLGGs harboring FGFR1 kinase hotspot mutations (FGFR1-N546K or -K656E) frequently harbored a second alteration associated with activation of the MAPK or mTOR pathways, most commonly in the phosphatase PTPN11, NF1 or within the FGFR1 gene itself. Additionally, we observed two previously described structural variants of FGFR1, an FGFR1 internal kinase tandem duplication (FGFR-ITD) and a fusion with TACC1 (FGFR1:TACC1). The relative impact of the different FGFR1 alterations on oncogenicity, therapeutic response and resistance has not been previously explored. To address this, we have established mouse neural stem cell models overexpressing the structural variants and hot spot mutant FGFR1 alone or in combination with a second alteration. Immunoblotting revealed that the addition of a second alteration attenuated phosphorylation of ERK, AKT and S6 and influenced cell proliferation both in normal growth conditions and in absence of growth factor. Treatment with inhibitors of FGFR (Infigratinib) and MEK (Trametinib) revealed variable sensitivity both targeted therapies, suggesting that treatment of FGFR1 driven pLGG might require tailoring to the specific FGFR1 alteration.

LGG-49. SUBEPENDYMAL GIANT CELL ASTROCYTOMA ASSOCIATED WITH A CORTICAL TUBER: A CASE REPORT

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Subependymal giant cell astrocytomas (SEGAs) are circumscribed gliomas strongly associated with tuberous sclerosis (TS). TS, a rare genetic disorder caused by inactivating mutations in either of the TSC genes (TSC1/2), leads to upregulation of the mTOR pathway and consecutive cell growth. CNS manifestations other than SEGAs include cortical tubers, white matter glioneuronal hamartomas and subependymal nodules (SENs), which, although regarded as distinct morphological phenotypes, share certain histological characteristics including ballooned astrocytes and giant ganglion-like cells. SEGAs, thought to develop from the median ganglionic eminence (MGE), are most commonly located periventricularly. However, rare cases of extraventricular SEGAs have been reported. We report a case of a cortico-subcortically located SEGA in a TS patient. A two-month-old female TS patient with multiple cortical tubers presented with treatment-resistant epilepsy. A 4cm sized tuber located in the right temporal lobe, showing a transmantle sign on MRI but no typical imaging appearance of SEGA, was surgically resected. Histological evaluation revealed typical morphological characteristics of a tuber with dysmorphic neurons, balloon cells and calcifications in the cortex and adjacent white matter. Focally, a cortico-subcortically located, well delineated area with increased cellularity and morphological features of a SEGA was found. Single mitotic figures were detectable. Immunhistochemically, these cells were strongly positive for GFAP, vimentin, and nestin. Scattered S100-, NeuN-, MAP2- and SMI32-positive cells were present. No expression of class-III-b-tubulin and TTF1a was found. pS6 was expressed in a small fraction of cells. CD34 showed a dense capillary network within the lesion. This case is consistent with prior case reports of SEGA-tissue in tubers of TS patients. However, the SEGA tissue of this case did not display TTF1a-expression, characteristic for SEGAs and considered as a marker for cells originating from the MGE, thus implying a different cellular lineage.