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In the recent 5th edition of the WHO classification of CNS tumors, 'Astroblastoma, *MN1* altered' is recognized a distinct brain tumor type, occurring in children and young adults. Due to its rarity and novelty, little is known about clinical and molecular traits. Therefore, we initiated an international effort and collected tissue samples, clinical and molecular data from 176 patients with Astroblastoma, *MN1* altered, identified by their distinct DNA methylation profiles. DNA methylation-based *t*-SNE clustering analyses revealed that Astroblastoma, *MN1* altered tumors form one distinct main cluster (n=158) showing *MN1:BEND2* and single cases with *EWSR1:BEND2* fusions and a further adjacent, but distinct smaller cluster (n=18) mostly defined by *MN1:CXXC5* fusions. Both fusion partner-defined groups show a median age of 12 years but distinct copy-number aberrations, characteristically a gain of chromosome 5 in one third of the *CXXC5*-fused group and a loss of chromosome 16q in one third of *BEND2*-fused cases. As previously reported, a vast majority of Astroblastoma, *MN1* altered patients are female, which we confirm for the *BEND2*-fused group (85%). The *CXXC5*-fused group, however, shows 75% male patients. Interestingly, 9/10 tumors of the few male patients observed in the *BEND2*-fused group were all located infratentorially or in the spinal cord, whereas almost all female cases show a supratentorial location (85/87). Histologically, the *BEND2*-fused group was primarily reported as Astroblastoma (39%), whereas in the *CXXC5*-fused cases, 31% CNS-PNET and only 8% Astroblastoma histologies were originally assigned. Preliminary clinical analyses showed that the *BEND2*-fused group has a relatively good 5/10-year OS of 97%/89%, but a less favorable 5/10-year PFS of 48%/35%, in line with previous studies. Patients showing CXXC5-fused tumors (n=8) indicated 5/10-year OS and PFS rates of 83%/83% and 60%/60%, respectively. Additional survival and molecular analyses are being conducted to further characterize Astroblastoma, *MN1* altered tumors and its molecular subgroups.

RARE-16. DIFFERENTIAL EXPRESSION OF MIRNAS IN ADAMANTINOMATOUS CRANIOPHARYNNGIOMA REVEALS DYSREGULATION OF PATHOGENIC PATHWAYS

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MicroRNAs (miRNAs) are small non-coding RNAs that regulate the expression of target mRNAs and can control whole gene networks. ACPs are benign pituitary tumours that can result in significant morbidity and premature mortality. ACPs harbour mutations in CTNNB1 and are driven by the activation of the WNT/beta-catenin pathway. We sought to explore the expression of miRNAS in adamantinomatous craniopharyngioma (ACP) in a cohort of samples previously subjected to RNA-Seq analysis (Apps et al, Acta Neuropathologica, 2018, May;135(5):757-777). Total RNA ACP samples (n=18), non-functioning pituitary adenomas (n=3) and normal foetal pituitaries (n=3) underwent miRNA sequencing using the Qiagen miRNA library prep kit on a NextSeq 500 to a depth of 16 million reads. Differential expression was performed using DESeq2 and functional analysis with mirPath v.3. Expression of miRNAs was correlated with previously published mRNA expression We found that 210 miRNA were upregulated and 275 down regulated in ACP compared with controls (adjusted p-value <0.1). MIR-205-5p was the most upregulated miRNA (619 fold) and its expression correlated with genes expressed within the tumour epithelium (e.g. TP63). miR-375 an inhibitor of the WNT pathway was the most down regulated miRNA (361 fold). KEGG Pathway analysis identified Glycosphingolipid synthesis as the most enriched pathway targeted by upregulated miRNAs. Pathways that were enriched by down regulated miRNAs included: ECM-receptor interaction, fatty acid biosynthesis, Hippo, TGF-beta, WNT, and ErbB pathways. Down regulation of miR-132 has previously been suggested as a marker of aggressiveness in ACP, and was 16 fold down regulated (adjusted p-value<0.001) in this cohort and expression was inversely correlated with genes relating to epithelial development. This data confirms previous studies indicating that miRNA expression is altered in ACP. In silico analysis suggest that the dysregulation of miRNA affects the expression of genes involved in pathogenic pathways in ACP.

RARE-17. MULTI-INSTITUTIONAL CRANIOPHARYNGIOMA COHORT HIGHLIGHTS NEED FOR MORE COMPREHENSIVE DATA COLLECTION ON COMORBIDITIES AND QUALITY OF LIFE

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BACKGROUND: Pediatric craniopharyngioma is associated with long-term survival, but tumor- and therapy-related complications often negatively impact quality of life (QoL). Standard treatments include resection and radiation, but institutional practices vary and recurrence rates remain high. In this review, we utilized a cohort from the Children's Brain Tumor Network (CBTN) to evaluate outcomes for craniopharyngioma. METHODS: CBTN provides clinical and genomic data for pediatric patients diagnosed with primary central nervous system tumors across 25+ institutions. We collected data for 124 patients, ages 0-21, diagnosed with craniopharyngioma between 2012-2020. Variables collected included treatment, recurrence/progression, and comorbidities. RESULTS: Excluding patients without confirmed pathologic diagnosis (n=10) or follow-up data (n=39), 75 patients remained. For initial treatment, most (n=46, 61%) received surgery alone (9 partial, 33 near-total resection). Twenty-six (35%) underwent both surgery and radiation, with 9 receiving both therapies upfront and 17 receiving radiation at progression/recurrence. Four (5%) patients received chemotherapy. Over half of the cohort (n=39, 52%) had at least one progression/recurrence, and four died (5%). Significantly higher rates of progression/recurrence (84% vs. 32%, p=4.0e-5) were identified in patients that had surgery and radiation, compared to surgery alone. Time to recurrence, progression, or death was shorter for the surgery and radiation group (HR=4.1, p<1.0e-4), and for those that underwent partial versus near-total resection (HR=2.7, p=0.1.2e-2). Comorbidities were likely underreported, based on low rates of visual (32%), neuroendocrine (27%), and neurologic (28%) deficits at diagnosis, and 29 patients (39%) with unspecified medical history. CONCLUSIONS: CBTN provides a robust repository of information on treatment and survival of craniopharyngioma patients. However, we found a paucity of data on associated comorbidities and QoL outcomes. We advocate that future datasets and clinical trials routinely collect functional outcomes alongside therapy and survival data, particularly in craniopharyngioma where long-term survival is balanced with future QoL.

RARE-18. PEDIATRIC CRANIOPHARYNGIOMA; SINGLE CENTER EXPERIENCE IN 246 CASES WITH DIFFERENT MANAGEMENT MODALITIES

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PURPOSE: To report our experience with different craniopharyngioma management strategies done for 246 patients in a single institution during a period of 14 years. METHODS: The medical records of all children with the diagnosis of craniopharyngioma treated at Children's Cancer Hospital Egypt (CCHE-57357) during the period from July 2007 to December 2021 were retrospectively reviewed. RESULTS : our registry included 246 pediatric craniopharyngiomawith median age of 7.4 years old. The main strategies of management after initial surgery were follow up, radiotherapy or administration of intracystic interferone post ommaya insertion. The number of cases in each group were 92, 147,and three respectively. Three patients were not operated upon because of heavily calcified lesions, two of them received radiotherapy while the third was kept under follow up. Overall gross or near total total excision was achieved in 31.2 % , subtotal resection was the case in 42.1% while Ommaya insertion and biopsy was done in 21.1 % of cases. Total number of patients received radiotherapy initially or on progression was 195 patients(78.9%). The five-year overall survival was 88% (95% CI 82.9 – 93.1) while 5- year progression free survival (PFS) was 49.2% (95% CI 41.2—57.2). The five-year PFS rates for patients in the follow up group versus radiotherapy group were 25.2% and 68.7% respectively (P< 0.0001). Beta catenin was positive in 76.4% of cases that were available for testing (123/161). CONCLUSION: management of craniopharyngioma should be individualized with the main objective is the quality of life. Conservative surgery which entails gross total safe resection whenever possible or lesser extent of resection followed by radiotherapy is the main strategy followed in our institution.

RARE-19. MOLECULAR CHARACTERIZATION AND TREATMENT RESPONSE OF METASTATIC DIA/DIG

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INTRODUCTION: Desmoplastic infantile astrocytoma (DIA) and desmoplastic infantile ganglioglioma (DIG) are glioneuronal tumors of early childhood. Surgical resection is usually sufficient to cure these benign

tumors. The presence of metastatic seeding is rare and has been reported as an adverse prognostic factor. We present 2 cases of young children with recurrent metastatic DIA/DIG to describe their presentation, therapeutic management and outcome and to highlight the importance of molecular characterization of these rare tumors to guide adjuvant therapy. CASES DESCRIPTION: The first patient developed metastatic recurrence after initial gross total resection (GTR) of a localized DIG. The disseminated relapse was treated with monthly carboplatin and vincristine (CB/VCR). Complete response was achieved after 15 cycles and the patient has remained in continuous complete remission for 5 years. Post hoc molecular analysis of the tumor revealed a BRAF-RDX fusion. The second patient presented with a disseminated intraventricular relapse following an incomplete resection of a DIA associated with a SPECC1L-NTRK2 fusion. The patient received 2 cycles of CB/VCR with minimal response and was then switched to Larotrectinib leading to a very good partial response (VGPR) 3 months into therapy and has remained on treatment since then with significant clinical improvement. DISCUSSION/ CONCLUSION: In our 2 cases, metastatic recurrence was responsive to adjuvant therapy leading to complete response with conventional chemotherapy in the first one and to VGPR with NTRK inhibitor in the second patient. Early molecular characterization of these benign tumors is critical in case of incomplete resection or metastatic seeding to widen therapeutic options and maximize chance of cure. Response with NTRK inhibitor appears rapid and significant but the total duration of treatment and sustainability of response after discontinuation remain unknown.

RARE-20. RETROSPECTIVE ANALYSIS OF 9 PINEOBLASTOMA

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BACKGROUND: Pineoblastomas (PBs) are rare, supratentorial, primitive neuroectodermal tumors. Little is known with the clinical features and outcomes of PBs. METHODS: We retrospectively analyzed consecutive patients with PBs who were treated in Guangdong Sanjiu Brain Hospital between December 2006 to May 2020. RESULTS: A total of 9 patients (7 males and 2 females) with PBs were treated in our hospital with a median age of 9 yrs (range: 1-36 yrs) at diagnosis. Total or near-total resection was achieved in 3 patients (33%), partially resection in 4 (44.4%),and biopsy in 2(22.2%). There were 4 patients have spinal cord metastasis at diagnosis. Five patients received craniospinal irradiation (CSI), with concurrent or adjuvant chemotherapy. The average total dose of CSI was 34.80±2.683Gy, and the average dose to local tumor bed was 56.08±6.41Gy. Two patients younger than 3 years old only received chemotherapy, while 1 patient did not receive any postoperative treatment, and 1 patients was unknown. The median followed up time is ? months(range:3-39 months). At the last follow up, 5 patients were died, 3 patients were survived, and 1 was lost to follow-up. The median OS was 31 months (95%CI 1.782-60.281). Disease progression occurred in 5 patients during the follow-up period, and the median PFS was 19 months. CONCLUSION: Pineoblastoma is a rare central nervous system malignancy with a tendency for disseminated disease. Comprehensive therapies such as surgical resection, radiation and chemo therapy are effective therapies for PBs.

RARE-21 *SOX2* PLAYS AN IMPORTANT ROLE IN CHOROID PLEXUS TUMOR DEVELOPMENT

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Choroid plexus (CP) tumors are rare primary brain neoplasms found most commonly in children and are thought to arise from CP epithelial cells. *Sox2* is a transcription factor that not only plays a role in development in the ventricular zone, CP, and roof plate, but also contributes to cancer stemness, tumorigenesis, and drug resistance. Gene expression studies demonstrate aberrant *Sox2* expression in human CP tumors, suggesting a role in tumor development. A subset of CP tumors exhibit abnormal NOTCH pathway activity. Using animal models, we previously show that sustained NOTCH activity leads to CP tumors. Immunofluorescence, RT-qPCR, and RNA scope assays have revealed increased *Sox2* levels in NOTCH-driven CP tumors compared to wild type CP in mice. To investigate the role of *Sox2* in CP tumors, we eliminated *Sox2* expression in NOTCH-driven CP tumors. Loss of *Sox2* almost completely blocked NOTCH-driven CP tumor growth in these mice, supporting a role for *Sox2* in these tumors. Ciliation regulation is one proposed functional pathway for tumorigenesis in CP tumors. Using immunofluorescence assays for cilia (ARL13b) and aquaporin transport protein 1 (AQP1) in combination with super resolution microscopy, we observe a stark contrast between wild type CP epithelial cells which are multiciliated and homogeneously express AQP1, indicative of normal epithelial differentiation, compared to NOTCH-driven CP tumors consisting of mono-ciliated cells with loss of AQP1 expression. In *Sox2*-deficient NOTCH-driven CP tumors, we observe tumor cells remain mono-ciliated and AQP1-negative, indicating that *Sox2* loss does not affect the ciliation machinery. Together this warrants further study into the mechanisms of *Sox2* functions in CP tumors. By unraveling the role of *Sox2* in CP tumors, we may better understand their origin and biology to ultimately design improved treatment options.

RARE-22 CHARACTERIZING THE LANDSCAPE OF STRUCTURAL VARIANTS IN ADAMANTINOMATOUS CRANIOPHARYNGIOMA

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INTRODUCTION: Adamantinomatous craniopharyngiomas (ACPs) are rare brain tumors that primarily occur in children and impact long-term morbidity and mortality. The canonical driver mutation for ACP growth occurs in *CTNNB1* and leads to constitutive activation of the Wnt/β-catenin signaling pathway. In this study, we outline the genomic, transcriptomic, and structural variant (SV) landscape in a cohort of 41 ACP samples. METHODS: We performed whole-genome sequencing (WGS) and RNA-sequencing of 41 ACP samples. Matched normal samples were also characterized by WGS. Mutect2 was used to detect single nucleotide variants (SNVs) and indels, and copy number data was generated using the GATK pipeline. SvABA was used to perform SV analysis and to identify significantly recurrent breakpoints and juxtapositions. DESeq2 was used to perform differential gene expression analysis based on clinical and molecular annotation data. RESULTS: 29/41 (70%) of the ACP samples harbored missense mutations in exon 3 of *CTNNB1*, all of which have previously been reported in ACP tumors. SV analysis identified a median of 11.5 events per tumor. Overall, 9.7% of events were interchromosomal. Of the remainder, the majority (78.6%) were deletions. No SVs occurred within *CTNNB1*. A positive correlation ($r = 0.533$) was observed between the frequency of SVs and SNVs within samples. Analysis of significantly recurring breakpoints (SRBs) did not identify recurrent breakpoint events. Differential gene expression analysis comparing samples with and without *CTNNB1* variants identified 2,143 differentially expressed genes with q-value < 0.05. CONCLUSION: This study identifies activating mutations in exon 3 of *CTNNB1* in a large cohort of ACP samples. We also integrate SV and transcriptomic data to comprehensively investigate ACP tumor genomes and identify putative novel tumorigenic mechanisms that advance our understanding of ACP biology.

RARE-23. PRESERVATION OF ENDOCRINE FUNCTION AFTER OMMAYA RESERVOIR INSERTION IN CHILDREN WITH CYSTIC CRANIOPHARYNGIOMA

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INTRODUCTION: Children with craniopharyngiomas (CP) can be subjected to significant morbidities caused by radical surgery and/or radiation with deleterious long-term consequences. Ommaya reservoir insertion (ORI) into cystic CP represents a minimally invasive procedure allowing immediate decompression and aims to avoid additional injuries. The purpose of this study was to determine the relevance of upfront ORI (+/- intracystic treatment) for preservation of endocrine function. METHODS: We performed a retrospective chart review of children with CP treated at the Hospital for Sick Children between 01/01/2000 and 15/01/2020 for review of endocrinological outcome after ORI. Endocrine function was reviewed at the time of initial surgery and throughout the course of follow-up. Event-free survival (EFS) was defined as the time to further surgical resection or irradiation. RESULTS: Seventy-nine patients were identified with a median age of 8.3 (range 2.1-18.0) years, 31 were males. Sixty-six patients underwent surgical treatment, including 41 ORI. ORI was performed as upfront treatment in 32 patients; 33 patients underwent gross total or partial resection and 1 patient radiotherapy as first treatment. Fifty-five of 79 patients had sufficient endocrine follow-up data. Endocrine function remained stable after ORI with a mean EFS of 27.64 (± 5.22) months. Surgical resection was associated with worsened endocrine function postoperatively with an EFS of 5.48 (± 1.74) months ($p < 0.001$). CONCLUSIONS: Upfront ORI (+/- intracystic treat-