An 18 month-old female presented with 4-months of weight loss, bilateral galactorrhea and constipation. Her weight decreased from the 15th to below the 1st percentile. CBC, celiac and thyroid studies were normal. Prolactin was at the upper limit of normal (25.8;ref 3.3–26.3). Breast ultrasound demonstrated symmetric breast tissue development. She was referred to pediatric gastroenterology for constipation and failure to thrive. Caloric supplementation, bowel regimen and barium enema were recommended. One week later, she was admitted with dehydration, painful constipation and further weight loss in the setting of an acute febrile illness. MRI revealed a normal pituitary and an intraventricular mass without hydrocephalus. She underwent gross total resection of the mass, later determined to be a choroid plexus papilloma. The patient's galactorrhea resolved abruptly following resection. Because of her galactorrhea, our patient underwent neuroimaging revealing an incidental mass without associated hydrocephalus. To our knowledge, precocious puberty and hyperprolactinemia have not been described in neoplasms distant from the pituitary. Thus, these lesions should be recognized as a potential etiology of precocious puberty and hyperprolactinemia.

RARE-50. TREATMENT RESPONSE OF CNS HIGH-GRADE NEUROEPITHELIAL TUMORS WITH MN1 ALTERATION

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BACKGROUND: CNS high-grade neuroepithelial tumor with MN1 alteration (CNS HGNET-MN1) are a rare entity recently described as a high-grade tumor containing a mixture of solid and pseudopapillary patterns with MN1 rearrangement. METHODS: CNS HGNET-MN1 patients were identified using genome wide methylation arrays across 5 institutions (the Hospital JP Garrahan, Hospital for Sick Children, the University Hospital Motol, Royal Children`s Hospital and Christchurch Hospital) and was correlated with treatment and outcome. Central imaging review with radiological features analysis was performed. RESULTS: We identified 9 patients harboring CNS HGNET-MN1 tumors through application of the Heidelberg brain tumor classifier. Seven tumors were T supratentorial and two in the spinal cord. Median age was 5 (range 3.6–14.6). All patients had surgery (6 GTR and 3 STR) as initial management followed by radiotherapy (focal 5/CSI 1) and systemic chemotherapy in 2 patients. Four of the 9 patients relapsed by 3 years post diagnosis, with 2 local and 2 metastatic failures despite complete surgical resections and radiotherapy. Three patients died due to tumor relapse after 24 months despite upfront radiotherapy. Seven of 9 patients had an initial diagnosis of ependymoma. CONCLUSION: Treatment of CNS HGNET-MN1 remains a major challenge with multiple failures, despite aggressive surgical resections and upfront involved field radiotherapy. Further multicenter, international prospective studies are required to determine the optimal treatment strategy for this group of tumors.

RARE-51. MOLECULAR INSIGHTS INTO MALIGNANT PROGRESSION OF CHOROID PLEXUS PAPILLOMA (CPP)

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Malignant transformation of CPP is rare and the mechanisms remain elusive. We report a case of progression of papilloma into carcinoma where we performed molecular sequencing of both samples. A boy was found to have a brain mass soon after birth. The gross total resection (GTR) was diagnostic of CPP. Six years later he developed a recurrent mass that demonstrated progression to a choroid plexus carcinoma (CPC). The patient received chemotherapy according to a "HeadStartII" protocol. He is 2.5 years off therapy and disease-free. A sequencing study consisting of 1700 genes and tumor transcriptome was done. The analysis of both samples revealed a germline variant of TP53(R248W) with LOH and an allele frequency of 39% in the germline sample, suggesting a mosaicism. Analysis of both samples identified extensive aneuploidy and similar pattern of gains in chromosomes 7/8/12/20/21/X. Copy number aberrations newly acquired in the carcinoma included copy gain of chromosomes 5q/12/15q/20, and copy loss of chromosomes 5q/13/22. The papilloma was found to harbor 3 somatic mutations with 4% to 21% allelic fractions, all lost in the carcinoma. These mutations were of unknown significance and with too low allelic fractions to be responsible for the transformation. More pertinently, chromosomal aneuploidy was significant with additional losses in the carcinoma. This resulted in the losses of two critical tumor suppressor genes, RB and BRCA2, playing a possible role in the observed transformation. The "HeadStart" experience suggested that the prognosis of TP53 mutant CPC may be improved in the absence of radiation therapy.

RARE-52. *RB1* GENE DELETIONS ARE THE NOVEL MECHANISM OF CHOROID PLEXUS TUMORS (CPT) ONCOGENESIS

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BACKGROUND: CPTs are known to be rare *TP53*-dependent neoplasms, while major molecular alterations underlying tumor progression, especially in *TP53*-wild type cases, are still unclear. METHODS: 18 primary CPT, including 16 choroid plexus carcinomas (CPC) and two atypical choroid plexus papillomas (CPP), were evaluated for copy number status of 87 major oncogenes and tumor suppressor genes by nCounter Cancer CNV assay by Nanostring and *TP53* and *RB1* by MLPA. Germline *TP53* nucleotide substitutions were analyzed by Sanger sequencing. RESULTS: Pathogenic germline *TP53* variants were present in 4 cases confirming Li-Fraumeni syndrome (LFS). Two patients have somatic *TP53* substitutions. Only one patient with LFS harbored somatic *TP53* deletion. In 7 patients, heterozygous deletions of *RB1* involving from 3 exons to the whole coding sequence detected by MLPA were discovered. All these findings were validated by nCounter CNV assay. Additionally, four patients have *WT1* deletions, two patients – *BRCA2*, and in 1 case - *NF1*, concomitant with *RB1* deletions in 3 cases. Interestingly, in one patient who faced a progression of CPP to CPC germline, *RB1* deletion was detected, and in both subsequent tumors, the length of the deleted region progressively increased. Notably, that *RB1* deletions are mostly mutually exclusive to *TP53* substitutions. 3 of 4 patients with *RB1* deletions having follow-up period >1 year faced with tumor-related adverse events. CONCLUSIONS: Somatic or uncommon germline *RB1* heterozygous deletions have been unraveled as a novel mechanism of aggressive CPT and could be implemented in prognosis definition schemes.

RARE-53. PINEAL PARENCHYMAL TUMOR OF INTERMEDIATE DIFFERENTIATION (PPTID) AND DICER1 SYNDROME: A CASE REPORT

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BACKGROUND: DICER1 syndrome is a rare inherited tumor predisposition syndrome linked to an increased risk of several malignancies. Affected individuals most commonly develop pleuropulmonary blastoma (PPB) and ovarian sex cord-stromal tumors. Brain tumors in these patients are rare, however; the increased frequency of pineoblastoma in this population has been established. Traditionally, pineal parenchymal tumors of intermediate differentiation (PPTIDs) have not been associated with DICER1 syndrome, with research suggesting alternative mutations driving tumorigenesis. These tumors are pathologically and clinically diverse, with long-term surveillance based on therapeutic interventions. Here we describe a case of a germline DICER1 mutation in a patient with a PPTID, suggesting that this mutation is not limited to pineoblastoma as previously reported. CASE: We describe a 19 year-old female with a WHO grade III PPTID treated with multimodal therapy including surgery, craniospinal irradiation (CSI) and chemotherapy. She was noted to have a thyroid mass at diagnosis and was subsequently diagnosed with a benign thyroid nodule, followed most recently by a cataract with pathology concerning for medulloepithelioma of the ciliary body. Due to the known association between medulloepithelioma and DICER1 syndrome, targeted germline sequencing was obtained and confirmed a pathogenic heterozygous mutation. CONCLUSION: To our knowledge this

is the first report of a PPTID in a patient with DICER1 syndrome. This association highlights the clinical implications of molecular evaluation in pediatric brain tumors, for both immediate therapeutic decisions and long-term surveillance.

RARE-54. MOLECULAR ANALYSIS OF ROSETTE-FORMING GLIONEURONAL TUMOR AT MIDBRAIN; REPORT OF TWO CASES

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Rosette-forming glioneuronal tumor (RGNT) is a tumor that primarily arises at posterior fossa. We experienced two rare cases of RGNT located at midbrain and investigated their molecular features. Case 1 is a 23-year-old female, and Case 2 is an 18-year-old male. Both cases were surgically removed by the occipital transtentorial approach. Histological analysis demonstrated a biphasic pattern of neurocytic and glial components. The former consisted of neurocytic rosettes and perivascular pseudorosettes, and the latter was GFAP positive, corresponding to the diagnosis of RGNT. Both cases have an excellent clinical course without receiving chemotherapy or radiation therapy. Small residual tumors of both cases shrunk and maintained for 27 and 12 months, respectively. Case 1 underwent DNA methylation array and a subsequent DNA methylation-based classifier, indicating that the case matched RGNT with a 0.99 calibrated score. Also, we identified FGFR1 K656 mutation. Pyrosequence analysis of other genes such as IDH1 R132, IDH2 R172, BRAF T599, BRAF V600, H3F3A K27, H3F3A G34, HIST1H3B K27, TERT C228, FGFR1 N546 had no mutations. RT-PCR of KIAA1549-BRAF fusion was not detected. DNA methylation status of Case 2 is under investigation. Pyorosequence analysis identified TERT C228 mutation but did not identify other mutations such as FGFR1 N546 and K656. Midbrain RGNT corresponds to the histological and molecular features of RGNT. RGNT needs to be differentially diagnosed in the case of a midbrain tumor.

RARE-55. CHALLENGES AND SPECIFIC STRATEGIES FOR CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY SYNDROME IN LOW RESOURCE SETTINGS. ON BEHALF OF THE INTERNATIONAL RRD CONSORTIUM IN LOW RESOURCE SETTINGS PANEL

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Germline biallelic mutations in one of the mismatch repair genes (MSH2/MSH6/MLH1/PMS2 results in constitutional mismatch repair deficiency (CMMRD), a condition associated with multiple tumors arising from multiple organs during childhood, and these individuals rarely reach adulthood. The paucity of information with respect to these conditions leads to mismanagement and may be a factor in the high mortality of patients with CMMRD. Two international consortia, the European CARE4CMMRD, and the international replication repair deficiency (RRD) consortium, are addressing the many challenges associated with this condition. To address specific issues surrounding the management of CMMRD in low and middle income countries (LMIC), a multidisciplinary taskforce of 11 specialists from nine countries was formed. Preliminary conclusions are: 1) Immunohistochemistry for CMMRD should be considered for all patients with suggestive clinical features. In countries where CMMRD is common, malignant gliomas, colon cancers and T cell lymphomas should be stained routinely as the prevalence of CMMRD in these tumors can exceed 40%. 2) Temozolomide should not be used in the management of malignant glioma. By contrast, preclinical studies have suggested increased sensitivity to nitrosoureas. For the management of CMMRD related lymphoma and leukemia, mercaptopurines should not be avoided or discontinued as a part of the standard of care before more data are collected. 3) Management with checkpoint inhibitors should be limited to centers with intensive care units and expertise in complex supportive care to manage side effects of immune therapy. 4) Surveillance protocols have demonstrated long term survival benefits and should be implemented in LMIC.

RARE-56. PERITONEAL SEEDING OF A DIFFUSE LEPTOMENINGEAL GLIONEURONAL TUMOR IN A CHILD

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Diffuse leptomeningeal glioneuronal tumors (DLGNT) are rare neoplasms of the central nervous system and have been included in the 2016 update of the WHO classification. This is the first description of a DLGNT disseminating to the peritoneal cavity via a ventriculoperitoneal shunt (VPS) in a child. We describe an 11-year old girl who received a VPS for a Dandy-Walker malformation at the age of seven, and was diagnosed with a spinal pilocytic astrocytoma with leptomeningeal metastases six months later. She received chemotherapy (SIOP-LGG protocol) with partial response, and had progressive disease eight months after therapy cessation. Following a novel biopsy, the diagnosis was revised to a DLGNT, with a KIAA1549-BRAF fusion and loss of 1p. She received vinblastine, but was clinically progressive and craniospinal radiotherapy was initiated. 13 months later, she suddenly presented with ascites. The inferior vena cava was compressed due to the ascites, and an abdominal drain was placed, with massive fluid release. Abdominal MRI indicated an omental cake and peritoneal contrast enhancement. Bone metastases were suspected in the iliac and femoral bones. Anatomopathological examination of the ascites showed an atypical cell population, with irregular, hyperchromatic and enlarged nuclei resembling the primary tumor. The cells were positive for synaptophysin, MAP2 and weakly positive for S100. Pan-NTRK staining was negative. The diagnosis of a metastatic localization of the DLGNT was made, due to seeding of tumoral cells via the VPS. Treatment with a MEK-inhibitor was initiated, but was stopped due to progressive disease and she died 3 weeks later.

RARE-57. PEDIATRIC CHORDOMA: WHOLE EXOME SEQUENCING OF 11 PEDIATRIC CHORDOMA SAMPLES

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Chordoma is a rare tumor and while *SMARCB1* alterations have been observed in poorly differentiated chordomas, conventional chordomas are not well understood. We interrogated nuclear and mitochondrial genomes of 11 chordoma samples from 7 children. Frozen tumor tissue DNA was extracted and whole exome libraries generated using Agilent SureSelect Human All Exon V6 kit plus mtDNA genome capture kit. Libraries were sequenced using Illumina Nextseq 500. MuTect2, VarDict and LUBA variant callers were used with allele frequency cutoff 2%. Potential germline variants were filtered bioinformatically. In total, 656±74 high-confidence somatic variants, including 368±43 nonsynonymous variants per sample were detected. Of 2,607 combined unique nonsynonymous variants, 95% were missense. Remaining high impact variants were frameshift (37%), stop gain (39%), splice acceptor/donor (22%), start and stop loss (2%). Of the unique nonsynonymous variants, 137 fall within Cosmic Cancer Census Genes, including high impact variants in *SETD2, MLLT4*. No previously reported *TBXT*, *CDKN2A*, *PI3K*, *LYST* mutations identified. Tumor Mutation Burden/Megabase was 10±1. The mitochondrial analysis revealed heteroplasmic m.11727C>T *MT-ND4* missense variants in three tumors resected at different time points from the same patient, and another heteroplasmic m.1023C>T rRNA mutation from the primary and recurrent tumors of another patient. Intriguingly, two Children's Brain Tumor Tissue Consortium patients with chordoma had identical heteroplasmic m.10971G>A *MT-ND4* nonsense mutations. Pediatric chordomas appear to lack somatic nuclear mutations. Observing recurrent mitochondrial mutations across multiple tumors from the same and/or different patients is striking, suggesting they may be implicated in tumorigenesis and be potential diagnostic markers.