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BACKGROUND: Constitutional mismatch repair deficiency syndrome (CMMRD) is a severe cancer predisposition syndrome resulting in early onset central nervous system (CNS) and other cancers. International guidelines for surveillance exist but no study has systematically evaluated the efficacy of this protocol. METHODS: We surveyed all confirmed CMMRD patients in the International Replication Repair Deficiency Consortium. A surveillance protocol consisting of frequent biochemical, endoscopic and imaging (CNS and total body MRI) studies were employed. Survival analyses and efficacy of each method were assessed. RESULTS: Surveillance data were collected from 105 CMMRD individuals from 41 countries. Of the 193 malignant tumors, CNS malignancies were the most common (44%). The surveillance protocol uncovered 49 asymptomatic tumors including 16 glioblastomas and medulloblastomas. Five-year overall survival was 89% for tumors discovered by surveillance, and 61% for symptomatic tumors (p<0.004). Similarly, 5-year survival was 82+/-11% and 24+/-6% for surveillance and non-surveillance of brain tumors (p=0.005). Yearly total body and q6 month brain MRI detected asymptomatic cancers in all but 3 symptomatic CNS gliomas. These were tumors uncovered when time between scans was >6 months as per protocol. Finally, of the low grade tumors identified asymptomatically, 5 were low grade gliomas. All of the low grade gliomas, which were not resected transformed to high grade tumors at a median of 1.6 ± 0.9 years. CONCLUSION: These data support a survival benefit in CMMRD patients undergoing a surveillance protocol. Adherence to protocol and resection of lower grade lesions may improve survival for patients with CNS tumors.

RARE-18. GENETIC EVALUATION IN PATIENTS WITH CHOROID PLEXUS TUMORS

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INTRODUCTION: Choroid plexus tumors (CPT) are rare intraventricular neoplasms of epithelial origin. They usually occur in the 2nd year of life, corresponding to 0.4–0.6% of intracranial tumors in this age group. They are sub classified, according to WHO 2016, in choroid plexus carcinoma (CPC), atypical choroid plexus papilloma (ACPP) and choroid plexus papilloma (CPP). Li-Fraumeni syndrome (LFS) is present in 50% of patients with CPC. In Brazil, the *TP53* p.R337H mutation affects 0.3% of the population in the South/Southeast. OBJECTIVE: Evaluate the incidence of genetic mutations in patients with choroid plexus tumors and therefore the importance of genetic evaluation. PATIENTS AND METHODS: Between 1992–2019, 38 patients were diagnosed with CPT in our institution, 23 with CPC. From 2012, 21 patients were referred for genetic evaluation, 16 of which had CPC (2 had previously CPP). Positive family history for neoplasms was present in 87.5%; 37.5% compatible with LFS, 50% of them with mutations. All the patients with positive, but unspecific, family history of neoplasms, had pathogenic mutation. The molecular investigation of the *TP53* gene in patients with CPC was performed and positive in 56.2%: R337H (5 patients), R110C, R158H, H179R, R196* (1 patient each). Of those with R337H, p53 protein immunohistochemistry resulted in 90–100% positivity. One of the patients with CPP that evolved to CCP had the H179R mutation. Clinical course was similar among them, and with those without mutations. CONCLUSION: These results confirm the need for genetic evaluation in patients with choroid plexus tumors for adequate therapeutic management and long-term follow-up.

RARE-19. PEDIATRIC HIGH GRADE GLIOMA WITH DNA REPAIR PATHWAY ABERRATIONS, CLINICAL CHARACTERISTICS AND OUTCOME

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DNA mismatch repair machinery is an integral part of the human genome and its defect has been involved in tumorigenesis and treatment resistance. Heterozygous monoallelic germline loss of function in MLH-1, MSH-2, MSH-6 or PMS-2 is involved in Lynch syndrome, whereas biallelic mutations cause constitutional mismatch repair deficiency (CMMRD) which is associated with hematologic malignancies and glioblastoma. We report here the clinical characterization and molecular analyses of 7 patients who presented with gliomas and MMR machinery aberrations. Two patients had a clinical diagnosis of NF-1 with dermatologic stigmata, of whom one patient has CMMRD and the other has Lynch syndrome. Two patients had a known family history of Lynch syndrome upon their diagnosis of glioma. Three patients with high-grade glioma and negative family history, 2 had germline mutations in MMR genes, and one had numerous mutations including MMR genes with microsatellite instability. Patients were initially treated with chemotherapy and radiation for high-grade gliomas (HGG); 5/7 had progression. Median time to progression was 12 months (range: 5–52), and median time from progression to death was 7 months (range: 2–25). One patient had low-grade glioma initially but progressed to HGG and is currently on therapy. Another patient treated with temozolomide and radiation is currently receiving maintenance therapy without any disease recurrence. Although the literature data on brain tumors with MMR deficiency is limited, these consistently show that MMRD-associated gliomas are treatment-resistant and have a dismal outcome. Collaborative efforts are needed to better understand this subgroup of pediatric HGG and to define optimal treatment strategy.

RARE-20. MALIGNANT PERIPHERAL NERVE SHEATH TUMOR OF A CRANIAL NERVE IN AN INFANT WITH NEUROCUTANEOUS MELANOSIS

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At one month of age, a female presented with a giant congenital nevus along lower back and thighs and hydrocephalus. A ventriculoperitoneal shunt was placed. An MRI was done at six months, initially reported as normal. At eleven months of age, five months after original MRI, patient presented with dysconjugate gaze and lethargy. MRI showed new 3.8 x 3.7 x 3.4 cm right cerebellopontine angle mass extending into Meckel's cave and foramen ovale along with leptomeningeal disease extending from the mass along the entire length of the spinal cord. Retrospective review of prior MRI revealed subtle leptomeningeal enhancement concerning for neurocutaneous melanosis (NCM). Given the leptomeningeal disease, family elected for open biopsy and debulking of lesion instead of aggressive resection. Histologically, the mass showed hypercellular spindle cell neoplasm with mitotic activity and necrosis mixed with remnants of normal cranial nerve. GFAP was negative, excluding a glioma. HMB-45, MITF, panmelanoma, and Melan-A were negative, excluding melanoma. A negative myogenin stain ruled out ectomesenchymoma. S-100 protein and SOX-10 positivity with variable loss of staining for trimethylation of histone H3 K27 were indicative of malignant peripheral nerve sheath tumor (MPNST). Given the course of the mass, trigeminal nerve MPNST was presumed. Given the poor prognosis of intracranial MPNST and NCM, family elected to forgo treatment and was discharged with hospice. She died 25 days after surgery. Cranial nerve MPNST is rare. MPNST in patients with NCM has not previously been reported to our knowledge.

RARE-21. CANCER SPECTRUM IN GERMLINE SUFU MUTATION CARRIERS: A COLLABORATIVE PROJECT OF THE SIOPE HOST GENOME WORKING GROUP

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BACKGROUND: Little is known about cancer risk associated with pathogenic germline *SUFU* variants. METHODS: Data of all previously published and 25 still unpublished patients with a pathogenic germline *SUFU* mutation were compiled. RESULTS: 124 patients in 67 families were identified, most of them ascertained after the occurrence of a medulloblastoma (MB) or as part of Gorlin syndrome cohorts. Overall, 30 patients were healthy carriers and 94 patients developed a total of 129 tumors (up to 4 tumors/patient): 68 MBs, always as first tumor (median age at diagnosis: 1.5yr [0.1–5]), 22 patients with at least 1 basal cell carcinoma (BCC) (median 10/patient) (median age at first BCC: 43yr, [17–52]), 15 meningiomas (median age 43yr, [13–72]), 7 ovarian stromal/fibrous tumors (median age 12yr [5–34]), and 17 other tumors including 5 sarcomas (median age: 50yr [7–79]). Median age at last follow-up was 30yr. Nineteen patients died, including 11 from MB. Second malignancies were diagnosed

in 21 patients including 13 in MB survivors. Mutations were inherited in 58/66 (88%) of cases in which inheritance could be tested and de novo in 8. In 6/67 families (9%), >2 children were diagnosed with a MB. CONCLUSION: In this large cohort of germline *SUFU* mutation carriers, MB in infants is the most frequent tumor but the spectrum also includes typical Gorlin syndrome tumors (BCC, meningiomas, and ovarian stromal/fibrous tumors) either as first tumors or as second malignancies. This broad tumor spectrum and the high risk of second malignancies justify the implementation of specific cancer surveillance programs.

RARE-22. GERMLINE PATHOGENIC VARIANT C.1552G>A;P.E518K IN DGCR8 CONFERS SUSCEPTIBILITY FOR SCHWANNOMATOSIS AND THYROID TUMORS

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Germline mutations in *DICER1* cause a pleiotropic susceptibility syndrome characterized by the development of pediatric or early-onset tumors including pleuropulmonary blastoma, Wilms tumors, pineoblastomas, multinodular goiter (MNG) and thyroid cancers. Somatic mutations in the other two microprocessors *DROSHA* and *DGCR8* have been found in Wilms Tumors and pineoblastomas. We present here two families with peripheral schwannomatosis and thyroid tumors carrying a germline variant c.1552G>A;p.E518K in *DGCR8*. Family one had six affected members with early-onset MNG and five of them developed schwannomatosis. All five members were heterozygous for the variant. One of the carriers had also been diagnosed with a choroid plexus papilloma at 7 years old. The common second event in all tumors tested was the loss of chromosome 22 at the somatic level. In family two, a 35-year-old male was diagnosed with a peripheral schwannoma at the age of 12. Since then, he has developed seven extra peripheral schwannomas (one of which was an ancient schwannoma) and papillary thyroid cancer. *DGCR8* lies on chromosome 22q, adjacent to the three schwannoma genes: *LZTR1*, *SMARCB1* and *NF2*. The variant, c.1552G>A;p.E518K localizes to the first RNA-binding domain of *DGCR8* and structural modelling predicts that it abolishes proper binding of RNA. It is also a hotspot somatic mutation in Wilms tumors. Using miRNA profiling, we show that this variant disrupts global microRNA production and *DGCR8* mutated tumors show a specific miRNA profile different from *DGCR8* wild type tumors. These findings reinforce *DGCR8* as a novel susceptibility gene for schwannomatosis and thyroid tumors.

RARE-23. NOVEL NF1 MUTATIONS IN TWO OCCURRENCES OF GLIOBLASTOMA MULTIFORM IN A PATIENT WITH CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY SYNDROME

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Constitutional mismatch repair deficiency (CMMRD) syndrome is a rare cancer predisposition syndrome in children. Its main associated tumor types include brain and CNS tumors, hematologic malignancies, intestinal polyps and colorectal tumors, and other malignancies. Tumor genesis within this population is highly complex and poorly understood. We describe a case of a patient with two occurrences of glioblastoma multiforme (GBM), each with unique NF1 mutations. The patient is a female with CMMRD who was first diagnosed with GBM of the right frontal lobe in 2015. She subsequently underwent gross total resection, radiation to the field and concomitant and maintenance therapy with Temozolomide and Everolimus, due to high suspicion for NF-1. Genetic studies didn't show NF-1, instead revealing a diagnosis of CMMRD. Molecular testing of the GBM showed a high mutational burden and an NF1 mutation. Later, screening revealed stage IV colon cancer, for which she underwent subtotal colectomy, partial liver resection and chemotherapy. Molecular testing from the colon cancer found a hypermutant malignancy without mutations in NF1. Surveillance imaging detected a mass at the original site of her GBM, for which she had a resection. Notably, the genetic profile of the second tumor substantially different from the original tumor and the colon cancer sample, but had new mutations in NF-1. These findings highlight the significant variability in the genetic profiles of tumors in the context of CMMRD. It is also worth considering that NF1 is one of the first in a cascade of mutations leading to GBM in these patients.

RARE-24. LARGE CONGENITAL MELANOCYTIC NEVI AND NEUROCUTANEOUS MELANOCYTOSIS: A RETROSPECTIVE CASE SERIES

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Neurocutaneous melanocytosis (NCM) is a rare disease characterized by excessive proliferation and deposition of melanocytes in the leptomeninges and brain parenchyma, occurring in children with large congenital melanocytic nevi (LCMN). Manifestations of NCM range from asymptomatic CNS melanin deposition to cranial neuropathies, seizures, and hydrocephalus. Patients with NCM are at risk for malignant melanoma. We conducted a retrospective, single-institution study of patients with LCMN evaluated at Memorial Sloan Kettering Cancer Center from June 2000 to January 2020. Of 55 patients studied, 15 had no radiographic NCM, and 40 had radiographic NCM at initial evaluation. MRI findings included: focal melanocytosis (33), diffuse leptomeningeal disease (4), solid melanoma (3). Malformations were identified in 13, including arachnoid cyst (4), congenital hydrocephalus (4), Dandy-Walker malformation (3), and tethered cord (1). Twenty-one patients completed imaging once and were followed clinically. Seventeen with serial imaging (10 with focal melanocytosis, 7 with normal MRI) remained stable over a median 24-month follow up (range: 1–124). Six had suspected radiographic progression of NCM without melanoma. Malignant melanoma developed in 11 patients, 5 with focal melanocytosis on initial imaging. Median time from focal melanocytosis identification to melanoma diagnosis was 80 months (range: 18–200). Median age at melanoma diagnosis was 9.9 years (range: 1.1–25.3). Median survival from melanoma diagnosis was 9.1 months (range: 1–60.4). Focal NCM on neuroaxis imaging does not predict time to transformation to malignant melanoma. Serial imaging is not indicated in absence of disease-modifying treatment. Clinical follow up of at-risk individuals is essential in early identification of complications.

RARE-25. RETINAL ASTROCYTOMA MTOR INHIBITOR THERAPY IN TUBEROUS SCLEROSIS MOSAICISM

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INTRODUCTION: Everolimus is an inhibitor of mTORC1 (mammalian target of rapamycin complex 1), it is Health Canada and FDA approved for SEGA and renal angiomyolipoma in the setting of tuberous sclerosis complex (TSC). There is little data available in regards to this treatment of TSC associated retinal astrocytoma (RA). Although the behaviour of RA is often indolent or slowly progressive, aggressive behaviour with retinal detachment and neovascular glaucoma requiring enucleation has been reported in several patients. Definite TSC diagnosis is established when either two major features or one major and two minor features are present. Probable TSC diagnosis is established when one major plus one minor feature is present. METHODS: We report a child with probable TSC mosaicism, with negative serum NGS for TSC but RA and retinal achromic patch on the left. A left retinal peripapillary astrocytoma around optic nerve and very close to fovea was noted. There was concern that if it grew or there were to be any leakage it would cause visual impairment. This lead to therapy with everolimus 4.5 mg/m2/d aiming for level between 5 and 10 mcg/L. RESULTS: This boy has had a gradual reduction of the RA over the last 29 months, with healthy retina in the region no longer occupied by the lesion and preserved vision. He has tolerated therapy well with occasional mouth ulcers. CONCLUSION: mTORC1 inhibition is effective therapy to preserve vision in the setting of retinal astrocytoma and tuberous sclerosis mosaicism.

RARE-26. RETROSPECTIVE ANALYSIS OF PEDIATRIC CHOROID PLEXUS TUMORS

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