## NEUROFIBROMATOSIS AND OTHER PREDISPOSITION SYNDROMES

### NFB-01. CENTRAL NERVOUS SYSTEM TUMORS IN VON HIPPEL-LINDAU MULTISYSTEM DISORDER: ARE THERE PREVENTIVE APPROACHES TO ESCAPE TUMOR INITIATION AT A YOUNG AGE?

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In pediatric neuro-oncology, the likelihood of an underlying tumor predisposition condition should be considered for all types of brain tumors. The aim of this study was to report the dramatic history of a VHL Tunisian family with many affected adolescents presenting central nervous system hemangioblastomas among wich many died in their twenties and those who survived suffered from depression and suicide attempts. To provide optimal clinical care and genetic counseling to affected patients and their young relatives, we conducted a literature review to answer the major question for this family: are there any preventive approaches to escape tumor initiation in our at-risk relatives at young age? The onset of VHL syndrome at the index case of our Tunisian family was at the age of 40 years when she presented a blurred vision on the right, related to retinal angiomatosis. The evolution was caraterised by recurrent eye lesions, the development of multiple renal tumors and hemangioblastomas at the cerebral, cerebellar and cervical spinal cord levels with neurologic symptoms and various functional nervous sequels after neurosurgical resections. Familial features of VHL were present in half of her siblings (6 among 12). Her 2 adolescent sisters, dead at the age of 20, harbored cerebral hemangioblastomas, whereas 2 of her brothers who died respectively at the age of 21 and 47 years harbored respectively ocular angiomas and vertebral angiomas. A third 48 year-old alive brother harbored cerebral hemangioblastoma as well as renal cell carcinoma. Only preimplantation genetic diagnosis (PGD) to select unaffected embryos can be applied to prevent the disease. High-throughput methods such as microarrays and sequencing are available nowadays for late-onset disorders with genetic predispositions. Long term surveillance and timely preventive treatment of lesions are crucial for VHL disease carriers. Effective psychosocial support to vulnerable children and their families is also essential.

### NFB-02. MATERNAL HIGH-FAT DIET EXPOSURE INCREASES THE PROLIFERATION AND GLIAL DIFFERENTIATION OF THE CELLS OF ORIGIN FOR NF1-OPTIC GLIOMA

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Some pediatric cancers arise in the context of tumor predisposition syndromes caused by germline mutations in genes that regulate cell growth. The most common of these syndromes, Neurofibromatosis type 1 (NF1), results in the development of low-grade tumors of the optic pathway (optic pathway gliomas; OPGs) in ~15% of affected children. However, risk assessment for each individual child is difficult, as it is currently challenging to predict which children with NF1 will develop OPG. Emerging human population-based evidence has raised the possibility that patient-specific risk factors, including infant birth weight, may modulate the risk of glioma development. High-infant birth weight can be modeled in mice by maternal exposure to a high-fat high-sucrose (HFHS) diet. To address the hypothesis that maternal high-fat diet exposure will increase the risk of OPG formation through intrinsic effects on the putative tumor cell of origin, we evaluated the effect of maternal exposure to a HFHS diet on the proliferation and differentiation of these cells (neural stem cells within the third ventricular zone; TVZ NSCs). Progeny from obese dams (MatOb) exposed to HFHS diet during and preceding gestation demonstrated increased proliferation and glial differentiation of TVZ NSCs *in vivo*. Similar results were observed with gestational HFHS diet exposure (GE) that did not result in maternal weight gain, suggesting these effects were related to maternal diet rather than weight. These effects were not observed in NSCs from other regions of the brain, supporting the regional specificity of the effect of diet on these tumor-initiating stem cells. Finally, we found that maternal HFHS diet resulted in elevated levels of leptin and insulin, both of which increase the proliferation of TVZ NSCs. Taken together, these findings provide early experimental evidence that maternal environmental exposure affects developing neural stem cells relevant to the risk of glioma formation.

### NFB-03. NEUROLOGICAL MANIFESTATIONS IN CHILDREN AND ADOLESCENTS WITH NEUROFIBROMATOSIS TYPE 1 - IMPLICATIONS FOR MANAGEMENT AND SURVEILLANCE

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INTRODUCTION: We aimed to (1) characterize the spectrum of clinical phenotypes of NF1 in a random pediatric population, (2) correlate genotype with phenotypic expression for those with a genetic diagnosis, and (3) explore radiological features of NF1 in the central nervous system (CNS) by radiomics analyses to predict clinical course. METHODS: We performed a database search in the hospital information system of the University Children´s Hospital between January 2017 and December 2020 for patients with NF1 and evaluated the clinical phenotype by retrospective chart review. RESULTS: 75 children/adolescents were identified with suspicion/clinical diagnosis of NF1 (median age 10.0 years (range, 1.1-22.6); 35 female), confirmatory revised "diagnostic criteria" were met in 57 patients at the last follow-up. Per number of documented items, major signs were detected as 73/75 café-au-lait macules, 31/63 freckling, 38/71 neurofibromas (thereof 21 plexiform neurofibromas), 18/43 optic pathway glioma, 5/66 Lisch nodules, and two patients with sphenoid dysplasia. Genetic analysis (31/75) identified pathogenic NF1 variants in 27 patients. In 20/66 cases a parent met diagnostic criteria. Cognitive symptoms included developmental delay (28/68), learning deficits (12/48), attention-deficit hyperactivity disorder (3/53), and behavior anomalies (7/63). Classical unidentified bright objects were seen in 29/43, other intracranial tumors in 7/43, and cerebrovascular abnormalities in 5/43. Analysis of imaging features of the CNS in these patients will involve lesion segmentation and radiomics features. Symptomatic/progressive low-grade glioma necessitated neurosurgical resection (4/25) and/or chemotherapy (12/25). In 10/25 neuropsychological functions were assessed by the German neuropsychological basic diagnostic instrument. Until June 30th, 2021, one patient died of progressive plexiform neurofibroma. CONCLUSIONS: A wide range of neurological manifestations, including neuropsychological deficits, should raise the suspicion of NF1 in an unselected pediatric population. We expect imaging features of the CNS to better predict the clinical course and enhance decision-making.

### NFB-04. EVALUATING FOCAL AREAS OF SIGNAL INTENSITY (FASI) IN CHILDREN WITH NEUROFIBROMATOSIS TYPE-1 (NF1) TREATED WITH SELUMETINIB ON PBTC-029B

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BACKGROUND: Focal Areas of Signal Intensity (FASI) are T2 hyperintense benign lesions in children with NF1. They can mimic the appearance of low-grade glioma (LGG). Selumetinib has shown efficacy in treatment of NF1-associated LGG but treatment effects on FASI have not yet been described. METHODS: Patients with NF1-associated LGG treated with selumetinib on Stratum 3 of PBTC-029B were compared to age-matched untreated children with NF1-associated LGG at Cincinnati Children's Hospital Medical. FASI were defined by published criteria as T2 hyperintense lesions lacking mass effect, enhancement or T1 hypointensity. Lesion size was determined by cross-product of perpendicular measures in LGG and 1-3 FASI per subject. When multiple FASI were present, the sum of FASI cross-products was used. Change between baseline and the latest available measure within 4 months of control was assessed, insuring that selumetinib-treated subjects were still receiving therapy. RESULTS: Fifteen age-matched pairs were assessed (2.8-16.9 years and 60% were male). Initial FASI size was not different between groups (p=0.98; median [IQR]: 138.7mm2 [88.4-182.0] for treated subjects versus 121.6mm2 [79.6-181.9] for untreated subjects). Lesion change was measured over mean follow up of 18.9 + 5.9 months. Spider plots show decreased LGG size over time during treatment, but there was no consistent change in size among treated or untreated FASI. Comparing FASI size between paired timepoints showed no difference in change from baseline for treated subjects versus for untreated subjects (two-sided test; p=0.08). In subjects who received selumetinib, there was no correlation between change in LGG and change in FASI (r=-0.04, p=0.88). Using RANO criteria for FASI lesions, 2/30 (6.7%) subjects had partial response, 26/30 (86.7%) subjects had stable disease, and 2/30 (6.7%) subjects had progressive disease. CONCLUSIONS: While the sample size was limited, treatment with selumetinib did not reduce overall FASI size in children with NF1 and LGG.