LOW GRADE GLIOMAS

**LG-01. MULTI-FOCAL OR DISSEMINATED LOW GRADE GLIOMA IN CHILDREN: THE RILEY HOSPITAL FOR CHILDREN EXPERIENCE**

Marianna Horn1, Gilbert Vezina1, Brian Rood1, and Roger Packer1; INOVA Fairfax, Fairfax, VA, USA

Intracranial or spinal dissemination is commonly seen in intracranial malignant glioma, constituting a bad prognostic feature. Low grade gliomas (LGG) are the most common solid tumors in children and are considered non-malignant. However, leptomeningeal metastasis has been reported in these tumors as well. To date, there has been a paucity of information available about dissemination and survival in patients with LGG with multi-focal disease or spinal metastasis. We performed a retrospective review of all children diagnosed with low-grade glioma at Riley Hospital for Children over a span of 17 years (1974-2011). Of 429 patients identified with low-grade glioma, the incidence of multi-focal or metastatic disease was 4.2% (18 patients). The mean age of diagnosis was 5.44 years (range 0.17-15.61 years). The majority of the patients had pilocytic astrocytoma (88.8%). One pilomyxoid astrocytoma and one fibrillary astrocytoma was seen. Mean follow-up time was 76 months. 3 year overall survival rate was 94.4%. 5 year event free survival was 44.5% as 10/18 patients required radiation or chemotherapy and 2/18 patients had durable remission with chemotherapy therapy alone. Survival was worse in children under the age of 3 at diagnosis tended to have a higher risk for refractory disease. In conclusion, children with intracranial multi-focal or dissemination of LGG have a high risk of recurrence but maintain an excellent overall survival rate.

**LG-02. LONG-TERM EFFICACY AND TOXICITY OF BEVACIZUMAB-BASED THERAPY IN CHILDREN WITH RECURRENT LOW-GRADE GLIOMAS**

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Because definitive surgical resection or radiotherapy for low-grade gliomas (LGG) in children may be associated with severe and permanent side effects, medical management has taken a significant therapeutic role. The combination of bevacizumab and irinotecan has demonstrated encouraging radiographic and clinical responses; however, longer-term toxicity and response durability have not been described. Fourteen pediatric patients with multiply recurrent low-grade gliomas were treated with bevacizumab and irinotecan with at least twelve months of follow-up after completion of initial therapy. All patients had failed at least two prior treatment regimens; six had disseminated disease, and all had disease progression prior to starting bevacizumab. Patients received initial bevacizumab treatment at a median of 4.54 years (range 0.17-15.61 years). The majority of the patients had pilocytic astrocytoma (88.8%). One pilomyxoid astrocytoma and one fibrillary astrocytoma was seen. Mean follow-up time was 76 months. 3 year overall survival rate was 94.4%. 5 year event free survival was 44.5% as 10/18 patients required radiation or chemotherapy and 2/18 patients had durable remission with chemotherapy therapy alone. Survival was worse in children under the age of 3 at diagnosis tended to have a higher risk for refractory disease. In conclusion, children with intracranial multi-focal or dissemination of LGG have a high risk of recurrence but maintain an excellent overall survival rate.

**LG-03. PROFILE OF PATIENTS WITH LOW GRADE GLIOMAS: A STUDY FROM KUWAIT CANCER CONTROL CENTRE, KUWAIT**

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**BACKGROUND:** Low grade gliomas (LGG) constitute nearly 35% of all CNS tumors in the pediatric age group. Most common locations are cerebellum, optic pathways, mid brain and cerebrum. Primary treatment of LGGs is surgery. Kuwait Cancer Control Centre is the only comprehensive cancer centre in Kuwait. All patients of pediatric brain tumors are referred to the pediatric oncology unit at for further management. METHODOLOGY: This is a retrospective review of LGG cases who presented to the pediatric oncology unit between 1998 and 2011. Further management was decided according to the treatment policy of the unit. Of the patients traveled abroad for further treatment. RESULTS: During the study period, 28 cases of LGG were registered. There was male predominance with 64.3% males. The mean age was 9.5 years. Nearly 80% patients had symptoms of raised intracranial tension (headache / vomiting). Gait disturbances and visual symptoms were present in nearly 40% cases. Most common locations were posterior fossa (28%), followed by mid brain (25%). Majority had partial excision (75%), while complete excision was achieved in only 4 cases. Radiation therapy was used in 50% of cases, while chemotherapy was used in about 32% of cases. At the end of therapy, 50% of the patients achieved partial remission (PR), in 25% the status was unknown, as they refused to follow-up. Four patients who had complete excision were in complete remission (CR). At last follow-up, total of 9 patients were lost to follow-up, 7 (25%) had died due to progressive disease. Eleven patients (40%) were alive with disease. Only one patient was surviving without disease. CONCLUSIONS: Our results for LGG are inferior to the internationally published results. The main reasons are high numbers of partial or minimal excisions, incomplete treatment and lost for follow-up after completing the treatment.

**LG-04. HAND-HELD OPTICAL COHERENCE TOMOGRAPHY DURING SEDATION DETECTS VISUAL ACUITY AND VISUAL FIELD LOSS IN YOUNG CHILDREN WITH OPTIC PATHWAY GLIOMAS**

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**BACKGROUND:** Detecting visual acuity (VA) and visual field (VF) loss in young children with optical pathway gliomas (OPGs) can be challenging. Retinal nerve fiber layer (RNFL) thickness as measured by optical coherence tomography (OCT) has been considered a biomarker of VA/VF in older children with OPGs. Similar to VA/VF testing, younger children have difficulty cooperating with OCT. We investigated whether RNFL measures using hand-held OCT (HH-OCT) in younger children under sedation could detect VA/VF loss. METHODS: A cross-sectional sample of children with OPGs (NF1-related or sporadic) from a single institute in a longitudinal HH-OCT study. Patients were included in this analysis if they required sedation to complete their MRI, had successful HH-OCT imaging and visual symptoms were present in nearly 40% cases. Most common locations were posterior fossa (28%), followed by mid brain (25%). Majority had partial excision (75%), while complete excision was achieved in only 4 cases. Radiation therapy was used in 50% of cases, while chemotherapy was used in about 32% of cases. At the end of therapy, 50% of the patients achieved partial remission (PR), in 25% the status was unknown, as they refused to follow-up. Four patients who had complete excision were in complete remission (CR). At last follow-up, total of 9 patients were lost to follow-up, 7 (25%) had died due to progressive disease. Eleven patients (40%) were alive with disease. Only one patient was surviving without disease. CONCLUSIONS: Our results for LGG are inferior to the internationally published results. The main reasons are high numbers of partial or minimal excisions, incomplete treatment and lost for follow-up after completing the treatment.

**LG-05. CHANGE IN VISION AS A RESULT OF CHEMOTHERAPY IN CHILDREN WITH OPTIC PATHWAY GLIOMAS**

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**BACKGROUND:** Optic Pathway Gliomas (OPGs) represent roughly 65% of all paediatric optic pathway tumors. Despite the dominant role of
CHEMOTHERAPY IN THE MANAGEMENT OF THESE TUMORS, THERE IS A LACK OF WELL-DOCUMENTED OUTCOME STUDIES ANALYSING THE EFFECT CHEMOTHERAPY HAS ON VISION IN CHILDREN WITH OPGS. OBJECTIVE: DETERMINE THE UTILITY OF CHEMOTHERAPY IN MAINTAINING VISION IN CHILDREN WITH OPGS. METHODS: A RETROSPECTIVE ANALYSIS WAS DONE ON ALL PATIENTS SEEN AT MONTREAL’S SAINTE-justine PEDIATRIC ONCOLOGY CLINIC, BETWEEN 1991 AND 2007, WHO WERE TREATED WITH CHEMOTHERAPY FOR AN OPG. PATIENTS WHO RECEIVED RADIATION THERAPY OR GROSS SURGERY AS RESECTION PRIOR TO CHEMOTHERAPY WERE EXCLUDED. RESULTS: SEVENTEEN CHILDREN WERE STUDIED. THE MEAN AGE AT THE START OF CHEMOTHERAPY WAS 3.24 YEARS. MEAN FOLLOW-UP TIME OF SURVIVORS FROM THE START OF CHEMOTHERAPY WAS 8.16 ± 4.69 YEARS. THREE PATIENTS DIED AS A RESULT OF THEIR OPG CHEMOTHERAPY WAS PREDICTIVE OF AN ANNUALIZED INCREASED RISK OF TUMOR PROGRESSION OVER SEVEN TIMES AS HIGH AS THE RISK OF PROGRESSING IN A CLINICALLY STABLE CHILD IN 24% OF CASES, SOLELY DUE TO OPTOMOTORILOGICAL SIGNS AND SYMPTOMS IN 24% OF CASES AND DUE TO A COMBINATION OF FACTORS IN 52% OF CASES. THE MOST COMMON CHEMOTHERAPY REGIME WAS CARBOPLATIN + VINCristine, FOLLOWED BY CARBOPLATIN ALONE, CYCLOPHOSPHamide ALONE AND CARBOPLATIN + VINCRISTine. DISEASE PROGRESSION AFTER CHEMOTHERAPY OCCURRED IN 76.4% OF CASES. RADIOTHERAPY WAS REQUIRED IN 47% OF CASES. PRIOR TO CHEMOTHERAPY, VISION IN BOTH THE BEST AND WORST EYE WAS SIGNIFICANTLY IMPROVED IN 5.9% OF EYES, REMAINED STABLE IN 64.7% OF EYES AND DECLINED IN 29.4% OF EYES. VISUAL ACUITY DID NOT SIGNIFICANTLY CHANGE FROM THE END OF CHEMOTHERAPY TO THE LAST KNOWN FOLLOW-UP. CONCLUSION: CHEMOTHERAPY IS MINIMALLY EFFECTIVE AT PRESERVING VISION IN CHILDREN SUFFERING FROM OPGS. DISEASE PROGRESSION AFTER CHEMOTHERAPY OCCURS IN THE MAJORITY OF CASES AND A SIGNIFICANT NUMBER OF CHILDREN EVENTUALLY REQUIRE RADIOTHERAPY.

LG-06. RESPONSE ASSESSMENT BY MRI IN CHILDREN WITH LOW GRADE GLIOMAS. RESULTS OF THE GERMAN COHORT CONSORTIUM SIOPLGG 2004 STUDY

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PURPOSE: Different methods of tumor measurement for response assessment have been published (1D, 2D and 3D) but it has not been tested if the results of assessment are meaningful for the prognosis of children with an LGG. PATIENTS AND METHODS: We selected out of the German patients of the HIT/SIOP LGG 2004-study children treated according to one chemotherapy arm. We identified 89 consecutive children with measurable tumors on MRI and calculated the percent change of the largest diameter, axial area, therapy arm. We identified 89 consecutive children with measurable tumors on MRI and calculated the percent change of the largest diameter, axial area, maximum diameter, axial area and reduction in tumor volume (after treatment and before). RESULTS: Mean age of all children was 5.2 ± 3.4 years. 40% of patients were NF1 status. Four patients died (5%) and 30 had progressive disease (34%). Kaplan-Meier analysis estimated an overall 5-year survival of 93%. Multivariable analysis indicated that change in tumor volume at 24 weeks was predictive of death (p = 0.03) of independent age (p = 0.26), gender (p = 0.12), NF status (p = 0.97). PFS was estimated to be 88% at 1 year, 75% at 3 years, and 56% at 5 years. Younger age (p < 0.001), non-NF1 (p < 0.001) and lower % volume change at 24 weeks (p < 0.001) were predictors of tumor progression. Median % reduction at 24 weeks was 4% vs. 33% for patients with and without progression, respectively (p = 0.01, Mann-Whitney U-test). Reduction in tumor volume <6% at 24 weeks was predictive of an annualized increased risk of tumor progression over 10 times higher. Changes in diameter and area were correlated with PFS, however the most informative were changes in volume at 24 and 54 weeks. CONCLUSION: In children receiving chemotherapy for an LGG the amount of volume change at 24 weeks is a strong predictor for progression and death.

LG-07. WEEKLY VINBLASTINE IS A THERAPEUTIC OPTION IN RECURRENT/REFRACTORY PEDIATRIC LOW-GRADE GLIOMAS

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BACKGROUND: In a majority of cases efficient treatment of low-grade gliomas in the pediatric population is achieved by surgery, sometimes accomplished by chemotherapy according to the LGG: SIOP 2004 protocol. However, some cases of LGG is refractory, treatment options in these cases often consists of LGG SIOP 2004 relapse protocol or radiotherapy. Vinblastine can be used as a secondline chemotherapy. METHODS: Four patients with refractory low grade glioma were given vinblastine intravenously. These patients had previously failed chemotherapy and/or radiation for unresectable low-grade glioma. Tumor location has differed, brainstem, 1, optic pathway, 1, thalamus, 1, cerebellum. Three of the patients were given vinblastine at a dose of 6mg/m2 weekly, the fourth patient received 5mg/m2 weekly. RESULTS: The treatment was given for at least 12 months in three of the cases. RESULTS: There have been significant reduction of tumor size in the 3 patients who have received vinblastine for at least 12 months. Response to treatment has been observed within three months interval with MRI. None of the patients have been forced to discontinue the treatment because of intolerable side-effects. The fourth patient has been treated for three months and follow-up with MRI indicates a slight reduction of tumor size. CONCLUSION: Vinblastine should be considered as a secondline chemotherapy in refractory low grade gliomas. Extended administration (> 12 months) seems to be tolerated well. If intolerable side effects dose reduction should be tried.

LG-08. EARLY CLINICAL AND RADIOLOGICAL RESPONSE OF RECURRENCE LOW-GR ADE GLIOMA TO BEVACIZUMAB AND IRINOTECAN - A CASE REPORT

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Low-grade gliomas (LGG) are the most common form of childhood brain tumor, the majority of all juvenile pilocytic astrocytomas (JPA). Unfortunately JPA in childhood frequently grow in brain areas unsuitable for gross total resections and further treatment is required. Radiotherapy is often contraindicated due to long-term sequelae; chemotherapy is growing in importance but for multiply recurrent glioma toxicity has to be evaluated. We decided to use bevacizumab and irinotecan because of the encouraging efficacy in childhood LGG described by Packer[1]. R.A. is a 6-years boy with a huge JPA involving hypothalamus and optic pathways. Partial resection was performed and two months later he started SIOP-LGG/2004 Protocol with Carboplatin-Vincristine. After induction therapy he experienced progressive disease with loss of vision and worsened visual fields so he underwent another resection with ophthalmologic improvement. A year later, after a MRI progression associated with loss of vision (Light Perception with the right eye and 1/10 of visual acuity with the left eye) we decided to start the Bevacizumab-Irinotecan regimen according to Packer’s publication [1]. Bevacizumab was given at 10 mg/kg every 2 weeks and irinotecan at 125mg/m2 every 2 weeks. A cycle of treatment was defined every two doses of the combination. No toxicity was reported, CT-scan after the first dose did not show any bleeding. After the third cycle the MRI showed a reduction in dimensions, with contrast enhancement being almost disappeared. The visual acuity improved to 9/10 (left eye) and Counting Finger (right eye) meanwhile the vision improved 20/200. Currently he is clinically in the central field of the left eye. We experienced an early clinical-radiological response to bevacizumab-irinotecan regimen, confirming that this could be a very effective regimen in children with LGG. Larger cooperative studies are needed to better assess efficacy and toxicity. [1]Packer RJ et al. Pediatr Blood Cancer 2009 Jul;52(7):791-5.

LG-09. BIOLOGY OF LOW GRADE PEDIATRIC GLIOMAS

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Low grade gliomas LGG are the commonest brain tumors in children and almost all have activation of the ERK/MAPK pathway. Usually this is due to a tandem duplication within chromosome 7q34 giving rise to a fusion gene involving BRAF and sometimes V600E mutation in BRCAF. Since these mutations are found in all LGG other mechanisms must be involved. Melanoma has BRAF mutations as well as mutations in GNAQ and GNA11. High grade gliomas in adults have mutations in IDH1 and IDH2. The role of these genes in pediatric LGG is unclear. We investigated 40 children with LGG and copy number (CN) variation of BRCAF in pediatric LGG. A total of 48 primary and 4 recurrent tumors (40 grade I and 8 grade II).
CN variation of BRAF gene was analyzed by real time PCR while point mutation analysis in BRAF was ascertained using MALDI-TOF mass spectrometer (sequenome). We looked for mutations in GNAQ209, IDH1, IDH2 and CIC. Results: We detected a point mutation of the BRAF gene in 18/47 samples, 14 of which were pilocytic astrocytomas (PA): 14/30 PA had increased CN of BRAF (47%). Only tumor location was significantly associated with increased CN: 62.5% of infratentorial tumors had increased CN versus only 25% of supratentorial tumors. The V600E BRAF mutation was found in 3 samples. A novel finding was the GNAQ209 mutation in 1 PA. No mutations were observed in GNA11, IDH1 or IDH2. All 3 samples with BRAF mutations had normal copy number, as did the GNAQ positive sample which also did not harbor a BRAF mutation i.e. these were mutually exclusive. The 4 samples taken from recurrent tumors showed the same molecular biology as the primary tumor. Targeted therapy for pediatric LGG is on the horizon. Drugs targeting the BRAF mutation are already in use in melanoma.

INTRODUCTION: Optic pathway gliomas pose a major management difficulty in NF1 and sporadic patients. Diagnosis and follow up are heavily based on multiple MR imaging. Currently, assessment of tumor volume and response to treatment is based on single slice linear measurements. Volumetric measurements, although considered the “gold standard” are rarely used in daily practice. The exact effect of chemotherapy on the gross total volume and internal composition of these tumors is therefore unknown. METHODS: We retrospectively reviewed MRI scans of 9 patients with anterior optic pathway gliomas that were treated between 2006-2011. Of our group, 5 patients have NFI, Average follow up time was 2.7 years (1-4 years). All patients received at least one line of chemotherapy. A total of 45 MR imaging studies were measured. Tumor measurements were done using our own novel algorithm. The gross total volume of the tumor was measured, as well as sub-segmentation including the solid enhancing, solid non-enhancing and cystic components. Pre and Post treatment volumes were carefully calculated. RESULTS: The gross total volume increased in an average of 27% during the follow up period. When excluding the cystic component, 14% enlargement was noted. Interestingly, the volume of the solid, non-enhancing component increased by an average of 40% while solid enhancing component decreased by an average of 15% following treatment. CONCLUSION: Over the follow up period, oncological treatment did not seem to have significant effect on gross total tumor volume in this selected group. Chemotherapy seems to have no effect on the solid non-enhancing component while slightly reducing the solid enhancing part of the tumor. Internal segmentation may aid in the evaluation of treatment-effects in OPG patients receiving chemotherapy.

INTRODUCTION: Current classification methods of optic pathway gliomas fail to fully represent the anatomical and biological variability of this complex entity. As a result, it is difficult to accurately predict the natural history, and select patients for individual treatment paradigms. The suggested classification system may facilitate a common language between subspecialties that are involved in the treatment and follow up of OPG. METHODS: PRINCIPLES OF THE PROPOSED CLASSIFICATION OF OPTIC PATHWAY GLIOMAS: Anatomy alone fails to represent the variability of OPG. The association with NF1, the age, histology and molecular biology are important components of any logical classification system. The following variables are included in our proposal for classification of optic pathway gliomas: 1 – Age, 3 – Histology, 4 - Molecular biology, 5 – Optic nerve involvement, 6 – Chiasmatic and extra chiasmatic tumor extent (by grading). CONCLUSION: The suggested new classification system is easy to use and may aid in pre-hoc stratification of OPG patients for the prediction of prognosis, evaluation of treatment results, and rational selection of new treatment modalities including surgery.

INTRODUCTION: Optic pathway gliomas are a major management difficulty in NF1 and sporadic patients. Diagnosis and follow up are heavily based on multiple MR imaging. Currently, assessment of tumor volume and response to treatment is based on single slice linear measurements. Volumetric measurements, although considered the “gold standard” are rarely used in daily practice. The exact effect of chemotherapy on the gross total volume and internal composition of these tumors is therefore unknown. METHODS: We retrospectively reviewed MRI scans of 9 patients with anterior optic pathway gliomas that were treated between 2006-2011. Of our group, 5 patients have NFI, Average follow up time was 2.7 years (1-4 years). All patients received at least one line of chemotherapy. A total of 45 MR imaging studies were measured. Tumor measurements were done using our own novel algorithm. The gross total volume of the tumor was measured, as well as sub-segmentation including the solid enhancing, solid non-enhancing and cystic components. Pre and Post treatment volumes were carefully calculated. RESULTS: The gross total volume increased in an average of 27% during the follow up period. When excluding the cystic component, 14% enlargement was noted. Interestingly, the volume of the solid, non-enhancing component increased by an average of 40% while solid enhancing component decreased by an average of 15% following treatment. CONCLUSION: Over the follow up period, oncological treatment did not seem to have significant effect on gross total tumor volume in this selected group. Chemotherapy seems to have no effect on the solid non-enhancing component while slightly reducing the solid enhancing part of the tumor. Internal segmentation may aid in the evaluation of treatment-effects in OPG patients receiving chemotherapy.
and is being closely monitored with serial ophthalmological examination and imaging. His visual acuity has remained stable. To our knowledge this is the first report of an optic pathway glioma in a patient with morning glory disc anomaly.

LG-14. VISUAL OUTCOME OF CHILDREN WITH NEUROFIBROMATOSIS TYPE 1 AND PROGRESSIVE OPTIC PATHWAY GLIOMA TREATED WITH CHEMOTHERAPY: PRELIMINARY REPORT FROM THE SIOP-LGG 2004 STUDY

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AIM: To report the visual outcome of children with Neurofibromatosis type 1 (NF1) and optic pathway glioma (OPG) entered into the SIOP-Low grade glioma (LGG) 2004 study and treated with chemotherapy (CT). PATIENTS & METHODS: 240 children affected by NF1 and progressive LGG were enrolled into SIOP-LGG 2004 study from June 2004 to December 2011. 205 children (85%) had OPG of which 58% were female, mean age at enrollment was 5.4 years (range 0.4-16.8). Main indications for treatment were threat to vision or progressive visual loss 75.6%. RESULTS: Visual acuity (VA) was classified as: “preserved” if visual acuity (VA) was more than 3/10 Snellen in both eyes, “partially preserved” if VA was above 3/10 in the best eye and vision was impaired or VA was below 3/10 in both eyes. The comparison between VA at enrollment and at the last follow-up (median 22.6 months) represents the visual outcome of these children. Paired VA data was available for 44 patients (21.5%). At start of treatment VA was “preserved” in 25%, “partially preserved” in 32% and “compromised” in 43% of children. At last follow-up visual function improved in 11%, remained stable in 70% and deteriorated in 18% and was classified as “preserved” in 23%, “partially preserved” in 14% and “compromised” in 45%. CONCLUSIONS: In this NF1 OPG cohort, ascertainment of visual performance was surprisingly poor. VA was compromised in 43% before treatment, CT was associated with stable visual function in > 2/3 of children but was infrequently associated with improved VA (11%). Whilst reliable testing of VA is possible with stable visual function in children of NF1 OPG cohort, ascertainment of visual performance was surprisingly poor, VA was compromised in 43% before treatment, CT was associated with improved VA (11%). Future studies will need to focus on this area.

LG-15. OPTIC PATHWAY GLIOMA TREATED WITH VINORELBIN: EXPERIENCE OF A SINGLE INSTITUTION

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Response criteria used a combination of magnetic resonance imaging, physical and visual evaluation. RESULTS: From the 34 patients with ULGG we evaluated 23 patients with diagnosis of OPG, 5 were assessable after 4 cycles of vinorelbine with objective response (OR, either partial or minor response) observed in 12. After 18 cycles, 16 patients were assessable for response showing 9 OR, 4 stable disease and 3 progressive disease. One patient died of atypical pneumonia. Grade III/IV hematologic toxicity was observed in 3 patients, grade I/II gastrointestinal toxicity in 2 and grade I neurotoxicity in 1. CONCLUSIONS: Vinorelbine is a valid option in the treatment of OPG with low toxicity and excellent quality of life. Future studies should consider oral vinorelbine as a potential option for children with low grade glioma.

LG-16. MULTISYSTEM BENEFIT OF SIROLIMUS IN TUBEROUS SCLEROSIS

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Tuberous Sclerosis (TS) is caused by mutations in the TSC1 or TSC2 tumor suppressor genes resulting in production of aberrant Hamartin and Tuberin. The clinical phenotype of TS results from the formation of benign tumors in multiple organs - brain, eye, heart, skin, kidneys and lungs. Subependymal giant cell astrocytomas (SEGA)s and facial angiofibromas are common and troublesome clinical features of TS seen in children. In the last five years there have been several reports of successful treatment of SEGA with Sirolimus and interestingly treatment with Sirolimus resulted in shrinkage of renal and Pediatric tumors. We report a 17 year old patient in whom treatment with Sirolimus produced improvement in bilateral mesencephalic SEGA and also almost complete clearance of severe adenoma sebaceum. The patient was diagnosed with SEGA in 2002 and showed asymptomatic progressive growth in 2011. His facial angiomases first appeared at 6 years and worsened with age. Treatment by laser had no lasting benefit. Since surgical resection involved risk of significant morbidity we started treating his SEGA with Sirolimus. Pre-treatment MRI showed multiple cortical and subcortical tubers, subependymal nodules and lobular SEGA’s prior to progression. Munro (L = 1.6 X 1.0 cm, R = 1.8 X 1.2). Initial dose was 7 mg per day which was later decreased to 6 mg, to maintain a serum level of about 10 ng/ml. The only adverse effects our patient experienced were isolated acneiform lesions and marginal hypercholesterolemia. Within one month his facial angiomases began to improve and by the time follow up MRI was done at 4 months his face was almost completely clear. The 4 month MRI showed significant improvement in the SEGA bilaterally (L = 1.2 X 0.9, R = 1.6 X 1.0). The authors would like to convey that the benefits of Sirolimus in TS may not be limited to the CNS/Kidney alone.

LG-17. PAEDIATRIC DIFFUSE GLIOMA WHO GRADE II: RISK FACTORS FOR SURVIVAL - REPORT OF THE HIT-LGG 1996 STUDY FOR PEDIATRIC LOW GRADE GLIOMA (LGG)

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Diffuse gliomas WHO grade II (DG2) were included in the multicentre study HIT-LGG 1996 to investigate their clinical course and risk factors for survival. DG2 was diagnosed in 72/1031 study patients (median age at diagnosis, 8.6 years, 32 female, 3 Neurofibromatosis). Thirty-four tumours were located in the cerebral hemispheres, 2 of 3 had primary dissemination. Gross total resection (GTR) was achieved in 16, subtotal/partial in 24, 32 patients had biopsy only. Histological diagnosis was diffuse astrocytoma grade II in 57 patients (39 centrally reviewed), oligoastrocytoma 3 (3) and oligodendroglia 10 (4). 43 patients remained observed, 28 following incomplete resection. Non-surgical therapy was started in 29 patients (16 biological activity, 12 chemotherapy). Overall survival of NFI-associated OPG will set VA as a primary outcome measure to ensure compliance with visual testing.
INTRODUCTION: Optic pathway gliomas (OPG) are usually considered relatively benign pediatric tumors. However, in the adult population they are a heterogeneous group of tumors with varying degree of malignancy. In general they can be roughly divided into two groups: adult patients with childhood (low-grade) tumors and very good prognosis and adult patients with adult (high-grade) tumors and less then favorable outcome. Each of these groups has its own unique characteristics, and should be treated and diagnosed accordingly. METHODS: We retrospectively accrued all adult patients with OPG that were followed in our center between the years 2000-2011. Various outcome measures including neurological, neuro-ophthalmological and oncological outcome were reviewed. RESULTS: Of 20 adult patients with OPG, 12 were included. Age at diagnosis varied widely (18-74), as was age at diagnosis with OPG (6m-66 years). Eleven of our patients are female, 12 have NFI, and 8 were diagnosed at adulthood. Two patients had a malignant pathology, 1 patient died from his OPG. Four patients had tumor progression as adult, 7 had visual deterioration. 6 patients were operated, 4 received chemotherapy and 2 received radiation. CONCLUSION: OPGs that present at adulthood tend to have a more malignant pathology and unfavorable course of disease. Adult patients with pediatric tumors may progress or suffer from visual deterioration. Long term clinical and radiological follow up is advised.

OBJECTIVE: We reviewed management and outcome of focal low grade brainstem tumors in 36 children. METHODS: We evaluated children treated for focal brainstem glioma (FBG) diagnosed between 1996-2010. Independent imaging review confirmed FBG with discrete lesions involving <75% of brainstem volume; each patient had histologically confirmed low grade glioma. Progression-free survival (PFS) and overall survival (OS) were determined. Univariate analysis assessed variables affecting PFS: age, sex, tumor location, growth pattern, tumor grade, treatment, and extent of resection. RESULTS: Fifty-six children were identified (n = 34 males) with an average age of 7.75 years (range, 1-17). Tumor location was: midbrain (n = 26), pons (n = 15) and medulla (n = 15). With median follow-up of 2.9 years, 24 children developed primary site local failure including 8 with metachronous high-grade malignancies within radiating fields at 5.3 and 10.3 months after radiotherapy (RT). Thirteen received RT following evidence of progressive disease within 25.1 months of diagnosis (median 4.2 months). Fourteen received RT after biopsy or resection; 11 of these began RT within 2 months of diagnosis due to clinical progression. Three began RT beyond a 2 month post-operative window (range, 11.2 - 45.6 months). Five patients died; two had disease progression; two developed infold short-interval high grade malignancies; one died without disease progression and presumed shunt failure. Surgical resection was the sole treatment in twenty-nine patients. Estimated 5-year PFS and OS were 59% and 98%, respectively. WHO Grade II disease showed improved PFS (p = 0.031); intrinsic tumors trended toward superior PFS (p = 0.058); no other factors impacted PFS. CONCLUSIONS: Assessment of clinical course, imaging and tumor biopsy describes a reasonable model for managing focal brainstem tumors. Surgery alone suffices in many children, with radiation reserved resection disease occurring within a 2 year window. Within the brainstem region, tumor sampling error and/or malignant transformation may have higher frequency, suggesting a role for stereotactic multi-pass biopsy.

INTRODUCTION: Tuberous sclerosis complex (TSC) is a genetic disorder associated to mutation in one of two tuberous sclerosis genes TSC1 (hamartin) or TSC2 (tuberin). Affected individuals may present with hamartomatous growths in multiple organs. Five to 20% of the cases develop neoplastic lesions of the central nervous system such as subependymal giant-cell astrocytoma (SEGA) which are slow growing tumors arising near the foramen of Monro. Because of the risk of acute hydrocephalus SEGA can be a cause of morbidity/mortality. Neurosurgical resection is the treatment of choice if the tumor grows after the age of diagnosis, however, the natural history, although survival for the subgroup of patients <2 or ≥ 11 years old appears impaired. GTR was associated with sustained OS and EFS with observation only, while incomplete resection and SML-location herald progression. PFS was not different between the treatment groups.

CONCLUSION: Everolimus therapy can induce regression of SEGA observed in the first 2 patients and hypercholesterolemia in the last one. CONCLUSION: Everolimus therapy can induce regression of SEGA observed in the first 2 patients and hypercholesterolemia in the last one. Additional cases are needed before this can be concluded. Future studies should attempt to disentangle the effect of everolimus from other factors that may contribute to SEGA regression in TSC patients.
LG-22. SIOP-LGG 2004 - COHORT DESCRIPTION OF A COMPREHENSIVE TREATMENT STRATEGY FOR LOW GRADE GLIOMA IN CHILDREN AND ADOLESCENTS INCLUDING A Randomized CHEMOTHERAPY TRIAL AND A RADIOTHERAPY TRIAL
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Low-grade glioma (LGG) in children and adolescents have a spectrum of presentations determining various therapies. The SIOP-LGG 2004 strategy recommends observation following complete resection or after incomplete surgery without severe or threatening symptoms, and age-stratified radio- and chemotherapy for patients with severe symptoms or later progression. The intensity of induction chemotherapy (2 vs. 3 drugs) is the randomised study question for sporadic LGG (NF1-ve). Multicentre radiology and path-ology reviews are integrated. Of 5200 patients registered from 01.04.2004 to 30.01.2012 in 12 countries, 1786 were observed, 1133 treated (35.5%), 66 in evaluation (221 incomplete data), 1340/2985 are males, 100/2985 disseminated, 453/2985 NF1 + ve. Main tumour localisation: supratentorial (48%), diencephal (12%), spinal (9%), only (29%), as well as glioblastoma (55%), anaplastic astrocytoma (22%), oligodendroglia (9%), medulloblastoma (5%), ependymoma (3%). Patients with mental age ≥1 year were NF1 + ve, 38% started treatment within 3 months/60%. Radiotherapy was used in 181 patients (median age 10.1 years), 26% were NF1 + ve, 35% treatment started within 3 months, 40% in 60%. Radiotherapy was used in 181 patients (median age 10.1 years), 4% were NF1 + ve, 38% started treatment <3 months. Distribution of tumour sites, extent of resection and histologies was comparable in the two treatment arms. Median progression-free survival (PFS) was 7.7 years (7.7%); 28 (71.8%) had local disease, 10 (25.6%) had disseminated disease. Main treatment was CR in 2 (5.1%), PD in 9 (23.1%), PR in 2 (5.1%), and SD in 1 (2.6%). Median length of survival was 7.7 years. 22 (56.4%) had Neurofibromatosis 1 (NF1), 2 (5.1%) had NF2, and 3 (7.7%) had NF1 + NF2. Survival is 99.3% for children being observed and 85.8% for those selected for non-surgical treatment. This European trial for childhood LGG providing therapy-guidelines as well as randomisation for a subgroup has high patient recruitment and adherence to the multi-disciplinary strategy including age stratification. Data quality control measures are in progress.

As her IGF-1 levels normalized, Pegvisomant was titrated from daily to every fourth day. The patient completed fifty-two weeks of Vinblastine and is doing well with stable disease (OPG and BSG). She remains on Pegvisomant every fourth day. CONCLUSION: The good response to this patient’s BSG to the combination of Vinblastine/Pegvisomant raises the possibility that GH excess may have a role in the progression/chemosensitivity of glomas. Further investigation is warranted.

LG-24. OUTCOME OF CHILDHOOD OPTIC PATHWAY TUMORS - EXPERIENCE OF KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE, RIYADH, SAUDI ARABIA
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BACKGROUND: Natural course and outcome of optic pathway tumors (OPT) has led to considerable variability in management. METHODS: A total of 39 patients (< 15 years) underwent treatment for OPT at our institution from 1997 to 2008. Twenty-two (56.4%) were female. Median age at diagnosis was 2.8 years, 22 (56.4%) had Neurofibromatosis 1 (NF1). RESULTS: Optic nerve was involved in 28 patients (71.8%) followed by optic chiasm in 5 (12.8%), hypothalamus in 3 (7.7%) and suprasellar in 3 (7.7%). Twenty-eight (71.8%) had local disease, 10 (25.6%) had dissemination within the brain and 12 (2.6%) had metastasis to the spine. Proposis was the most common presenting symptom in 19 patients (48.7%), followed by diminished vision in 8 (20.5%) and vomiting in 7 (17.9%). A total of 17 patients (43.5%) underwent surgical resection, 9 (23%) were observed only, 9 (23%) had observation periods prior to or after other forms of therapy (12,30.8%) received neo-adjuvant chemotherapy; 3(7.7%) adjuvant-chemotherapy; radiotherapy 3(7.7%). Results of first line treatment was CR in 2(5.1%), PD in 9(23.1%), PR in 2(5.1%), and SD in 23(60.6%). Vision improved in 5 patients (12.8%), 2 (5.1%) had progressive development (6.9%), as well as gliomatosus LG. 16(41%) were blind. Overall survival (OS) and event free survival (EFS) at 10 years were 100% (41%) respectively. Twelve (30.8%) had PD, 6/12 had NF1 after first line therapy and all stabilized after second/third line treatment.12(6.9%) developed Anaplastic Gliomas. 16(41%) experienced no event. For those 30 patients who required treatment, OS was 100%. The EFS was 60% and 33.4% at 5 and 10-years respectively. Of theses, 23(76.7%) are on follow-up after finishing treatment, 6(20%) are on treatment and 1(3.3%) on palliative care. CONCLUSION: OPT have a heterogeneous behaviour and their inherent natural history has led to different modalities of therapy. Despite long term survivals many children have impaired vision.

LG-25. DYNAMIC CHANGES IN LONG-TERM VISUAL OUTCOME AFTER TREATMENT OF CHILDREN WITH NF1 OPTIC PATHWAY GLIOMAS
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INTRODUCTION: Long-term visual outcome following chemotherapy for optic pathway gliomas (OPG) in children with neurofibromatosis type 1 (NF1) is unknown. We previously reported visual acuity (VA) outcomes at completion of initial chemotherapy in 88 children with NF1-OPG; 32% improved, 40% remained stable, and 28% declined. We now report VA outcomes 3 years after completion of initial treatment. METHODS: A retrospective, international multi-center (N = 10) study evaluated visual outcomes following initial treatment with NF1-OPG. Subjects received first line treatment with chemotherapy between January 1997 and December 2007. RESULTS: 59 subjects were evaluable for 3-year VA outcome. As measured from start of initial treatment, the 3-year post-treatment VA was improved (31% of subjects), stable (42%) or worse (27%), suggesting that VA remained unchanged after completion of initial therapy. However, when
measured from the end of therapy, VA remained stable in only 47.5% of subjects at 3 years. 22/59 (37.2%) required additional therapy in the intervening 3 years. Approximately 1/3 of subjects who had VA improvement at the end of initial treatment continued to demonstrate improvement some relapsed and after subsequent treatment had VA outcome that surpassed VA after initial treatment; others (15%) received no further treatment, but had continued improvement in VA. 77% of subjects with worse VA at completion of initial therapy maintained the next 3 years half progressed during initial treatment and were changed to second-line therapy. The other half completed initial therapy with modest decrease in VA (median logMAR decrease = 0.25) and were never retreated; their VA drifted towards pre-treatment baseline over time without logMAR improvement = 0.20). CONCLUSIONS: Visual acuity in the 3 years following completion of initial chemotherapy continues to change in half of subjects with NF1-OPG, many of whom received no further therapy. Continued close observation after treatment is important, as visual outcome is a dynamic process.

LG-26. IS VISUAL ACUITY DETERIORATION THE ONLY INDICATION TO INITIATE THERAPY FOR NF1 ASSOCIATED OPTIC PATHWAY GLIOMAS

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INTRODUCTION: Indications for treatment of neurofibromatosis type-1 (NF1)-associated optic pathway gliomas (OPG) vary in the literature. Some advocate treatment for either radiographic or visual progression; others reserve treatment solely for patients with documented visual progression. METHODS: A retrospective, international multi-center (N = 10) study was undertaken to evaluate visual outcomes following chemotherapy in children with NF1-OPG and to ascertain indications for treatment. Subjects underwent initial treatment with chemotherapy between January 1997 and December 2007. RESULTS: As previously reported, visual acuity (VA) at completion of initial chemotherapy in 88 subjects was improved in 32%, remained stable in 40%, and declined in 28%. There was no difference (p = 0.2) in VA outcome between these groups with different treatment indications: VA deterioration + tumor growth (41%) worsened, VA deterioration without tumor growth (28%), and VA improvement without tumor growth (17%). In contrast, subjects with normal VA at the start of therapy (n = 18) appear less likely to have visual deterioration at completion of treatment than those with abnormal VA at baseline (11% vs 33%, p = 0.08). Moreover, the degree of VA decline in subjects who worsened on treatment was significantly greater (p < 0.0001) for subjects in the abnormal VA cohort (mean 0.79, median 0.59 logMAR) than those in the normal VA cohort (mean 0.19, median 0.20 logMAR). Only one subject in the normal VA cohort compared to 40% in the abnormal VA cohort required further therapy in the subsequent three years. Indications for treatment in the normal VA cohort included tumor progression (all 18), location (6), size/extent (5), and visual field loss (2). CONCLUSIONS: If VA is normal at the start of chemotherapy, the likelihood of treatment failure or subsequent significant vision loss is minimal. Although there are other reasons to initiate therapy, these findings suggest that caution should be exercised before recommending treatment for NF1-OPG with normal VA.

LG-27. ARE THE CONTRAST SENSITIVITY AND COLOUR VISION MEASUREMENTS USEFUL IN MONITORING OPTIC PATHWAY LOW GRADE GLIOMA

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Low-grade gliomas are a group of heterogeneous tumours that originate from glial cells and are well differentiated. Gliomas on the optic pathway (OPG) can cause optic nerve function dysfunction. A reduction in visual or radiological increase in size are indicators for treatment. In this prospective study spreading over 8 years, we analyse the use of 3-monthly contrast sensitivity and colour vision testing in monitoring the OPG. 14 patients were enrolled in the study over a period of 8 years, with 8 females and 6 males. The average age at diagnosis was 6.3 years ranging from 3 months to 14 years of age. The follow-up duration ranged from 2 to 8 years. 3 out of 14 patients had neurofibromatosis-1. 51% of the gliomas were meningiomas. 3 out of 5 NF patients, aged 4, 6 and 6 years, did not have lisch nodules. 10 out of 14 patients with OPG developed optic nerve dysfunction. In 10 out of 14 patients, visual acuity was the first function to get affected. In these patients, visual acuity continued to deteriorate until the visual function failed. This was followed by contrast sensitivity. 3 out of the above 10 patients later had a relapse. At this stage their visual acuity was below 6/24, and these patients had contrast sensitivity reduction that preceded visual acuity reduction and radiological change. All the three patients required treatment 3 months later. 4 out of 14 patients with OPG remained stable without requiring any treatment; 3 had NF-1 with 2 patients without Lisch nodule and two were male. We conclude that the colour vision and contrast sensitivity are not as sensitive indicators for monitoring as visual acuity, however, in patients with reduced vision contrast sensitivity may be helpful.

LG-28. DOES SITE OF OPTIC PATHWAY LOW GRADE GLIOMA AFFECT OPTIC NERVE FUNCTION

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We analysed our 8 year data of 157 patients with low grade glioma (LGG). 14 patients (8.9%) had the LGG affecting the optic pathway. According toDodici classification for optic pathway glioma, 4 out of 14 patients (28.5%) can be placed in group 1 (optic nerve), 6 out of 14 patients (42.8%) in group 2 (optic nerve chiasm) and 4 out of 14 patients (28.5%) in group 3. 2 patients in group 1, one patient in group 2 and one patient in group 3 did not have any optic nerve dysfunction. The two patients in group 1 and the one patient in groups 2 had neurofibromatosis-1. 2 out of 4 (50%) patients in group 1, 5 out of 6 (83%) patients in group 2 and 3 out of 4 (75%) patients in group 3 had optic nerve compromise. We conclude that in patients with OPGs, patients in group 2 and 3 had more optic nerve function compromise than patients in group 1.

LG-29. CHARACTERIZATION OF KIAA1549-BRAF FUSION RESPONSIVENESS TO SELECTIVE BRAF INHIBITOR

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Astrocytomas are the most common type of central nervous system tumor in childhood. A recent report has suggested that activated BRAF mutations, via the KIAA1549-BRAF fusion gene, are a key feature of low-grade astrocytomas. Utilizing several different cell lines stably expressing various altered BRAF and BRAF-fusion constructs we evaluated first and second-generation BRAF inhibitors including PLX4720 and PLX-PB compounds. In vitro kinase assays demonstrated the KIAA1549-BRAF fusion kinase, like V600E BRAF, undergoes inhibition in the presence of both first and second-generation selective BRAF inhibitors. However, KIAA1549-BRAF-fusion expressing cell lines were resistant to PLX4720 and displayed paradoxical activation to first-generation BRAF inhibitor suggesting distinct and cell-context dependent mechanisms for MAPK activation. In contrast, KIAA1549-BRAF-fusion-mediated MAPK activation was abrogated by PB-3, a second-generation, “paradox-breaking,” selective BRAF inhibitor. This suggests that pediatric low-grade astrocytomas harboring the KIAA1549-BRAF fusion may be responsive to second-generation BRAF inhibitors. Future studies are focused on understanding how KIAA1549-BRAF fusion signaling is mechanistically different than canonical V600E mutant and how this impacts the differential responses to selective BRAF inhibition.

LG-30. BRAINSTEM LOW GRADE TUMORS PRESENTING WITH BLOOD FEVER: A CASE SERIES OF A PRIMAL PUGILIST WITH BRAF V600E MUTATION AND SUCCESSFUL TREATMENT WITH VEMURAFENIB

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Low grade tumors of the brainstem are difficult to treat despite their benign pathologic appearance. Molecular alterations may contribute to this treatment resistance. Activating mutations in the BRAF gene are well characterized and found in pediatric low grade gliomas. We present our
data demonstrating an increased rate of Braf V600E mutations in low grade tumors of the brainstem and a case of a patient with a relapsed brainstem low grade glioma successfully treated with vemurafenib and vemlbacot after failure of radiotherapy. Seven brainstem low grade gliomas were directly sequenced to evaluate for the presence of mutations in the Braf gene. The presence of the Braf V600E mutation was detected in three with a unique mutation in the Braf gene identified in a fourth. Of these four patients, one died of disease progression, two have stable disease and one has had progressive tumor despite radiation. This patient initially received proton beam radiation to her tumor. She then presented 14 months post-radiation with new-onset dysphagia and persistent hiccups. Imaging demonstrated massive tumor progression. Given the dismal prognosis associated with relapse, she was started on vemurafenib, a Braf inhibitor which has been shown to have efficacy in the treatment of Braf v600e mutated metastatic melanoma. She has tolerated therapy well and after 14 weeks of treatment has demonstrated a marked improvement in her tumor burden without new dysphagia and near cessation of hiccups. Brainstem low grade tumors may arise as a result of unique molecular alterations. Our data demonstrate an increased presence of Braf v600e mutations in these patients which may contribute to tumorigenesis and resistant to therapy. As illustrated in this case, targeted inhibition of the Braf pathway may represent a new avenue for treatment of these difficult tumors.

LG-31. A DISTINCT GENE-EXPRESSION PROFILE IN PEDIATRIC GANGLIOGLIOMA
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Ganglioglioma (GG) is a well-differentiated neuro-epithelial tumor composed of both neuronal and glial components. Most GGs grow slowly, and are relatively benign in nature but occasionally, they display anaplastic features and undergo malignant changes. Because of its rare occurrence, little is yet known about the molecular pathology of this neoplasm and very few are the cytogenetic and molecular genetic studies reported. To better understand the mechanism underlying the development of GG, we performed gene expression analysis on 12 GG along with 10 pilocytic astrocytomas (PA) included as typical example of low-grade glioma. The identification of candidate probe-sets was performed by means of 1,121, a machine learning method based on regularization. QPCR analysis was then used in order to confirm and validate the results. This strategy succeeds in identifying a gene expression signature able to dichotomize PA vs GG. The signature consists of 103 probe-sets corresponding to 70 genes which encode adhesion, ECM-receptor interaction, matrix extracellular organization, neurogenesis (DLX1, DLX2), cell response (HRAS, MAPK1), cell cycle (CCNB2, CCNB1, CCNA), and metabolism (FABP5, FABP1, LDHA, ALDOA), some of which are the components of collagen gene family (COL1A1, COL1A2, COL3A1, COL5A1, COL6A2, and COL6A3), whose functions are associated with extracellular matrix (ECM) reorganization. It is noteworthy that, changes in expression of these genes controlling cell growth (IGF2, IGFBP6, LTBPs), cell motility (L1CAM, COL3A1, ITGA8) and interactions with the surrounding environment (LUM, COL1A1, COL6A3) POSTN appear to be linked to GG histotype. Our findings show the complexity and vitality of these tumors, shedding light on features such their richness in connective tissue. Additionally, they point to some interesting candidate genes worth further investigations.

LG-32. CLINICAL AND RADIOLOGICAL PREDICTIVE FACTORS OF CHEMOSENSITIVITY IN PEDIATRIC LOW GRADE GLIOMAS: A SINGLE CENTER STUDY
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INTRODUCTION: Not all low grade gliomas (LGG) will benefit from a carboplatin-based chemotherapy. A better understanding of factors predicting response to chemotherapy is essential to devise an optimal individualized treatment management. PATIENTS AND METHODS: Between January 1989 and December 2009, all patients with LGG treated with chemotherapy outside the StHMG protocol were considered for the study. We evaluated radiological tumor response of 82 LGG who received at least one course chemotherapy according three radiological assessment; three-dimensional (3-D), two-dimensional (2-D) and RECIST. We also correlate clinical and radiological response to EFS. RESULTS: Considering 3-D measurement as a gold standard, RECIST criteria was clearly unable to identify the responders and the non-responders appropriately while the discrepancy was minimal with 2-D assessment. A tumor response of at least 25% in 2-D (minor response according to MacDonald criteria) was marginally correlated to event-free survival. We therefore decided to consider it as the good response criterion. An homogenous contrast enhancement at diagnosis was identified as the main predictive factor of a good response to chemotherapy (p = 0.004). Although all patients who had radiological tumor progression had a worse clinical evolution, clinical response after chemotherapy was not correlated either to a radiological good response or a stable disease. EFS was worse in children younger than 1 year at diagnosis, with optic pathway gliomas, absence of NF1 status, presence of metastasis or multilencentric lesions. CONCLUSION: Tumor volume reduction can predict outcomes in children with LGG. Radiological response is associated with the radiological appearance of the tumor at diagnosis.

LG-33. LONG-TERM OUTCOME OF CENTRALLY LOCATED LOW-GRADE GLIOMA IN CHILDREN
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BACKGROUND: Optimal management of children with central, progressive symptomatic low-grade glioma (LGG) is unclear. Interventions widely used are chemotherapy in younger children and radiation therapy in older children. The risk factors at diagnosis and the effects of interventions on long-term morbidity are still undefined. We analyzed the impact of clinical characteristics, BRAF-KIAA1549 fusion and primary therapy on long-term morbidities and survival. METHODS: Medical records of patients with centrally located LGG diagnosed between 1987 and 2008 were reviewed. 47 patients were identified. RESULTS: Median age was 4 years and median follow-up was 79 months. The primary site was chiasm-hypothalamus in 33 (70%) and thalamus in 11 patients (23%). Seven (15%), 13 patients (28%), 27 (57%) underwent either surgery, radiation therapy or chemotherapy as initial intervention, respectively. The 5 year PFS for surgery, irradiation and chemotherapy groups were 71%, 76% and 37%, respectively (p = 0.02). The 5-year PFS for all patients was 53% and the OS 96%. Younger age group (0-4 yrs) showed significantly poor PFS (p = 0.03). Multivariate analysis showed initial chemotherapy (HR 4.9) and growth hormone deficiency (HR 3.1) were significantly associated with poorer PFS. Among children who progressed after chemotherapy and received radiation therapy the 2-year and 5-year PFS after salvage irradiation were 92% and 55%. The mean duration between diagnosis and radiation was 31 months. Fisher’s exact test showed significant association between age and endocrine abnormalities (p < 0.00001). BRAF-KIAA1549 fusion detected in 18 out of 27 (67%) samples was not associated with clinical outcome. CONCLUSIONS: Effective and durable tumor control was obtained with radiation therapy as initial treatment. In younger patients, chemotherapy can significantly delay the use of radiation therapy. However, frequent progressions with long-term morbidities are common in the young patient. More effective and less toxic therapies are required in these patients, the majority of whom are long-term survivors.

LG-34. OPTIC PATHWAY GLIOMAS IN CHILDREN: RETROSPECTIVE ANALYSIS OF 55 CASES. A SINGLE INSTITUTION STUDY
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BACKGROUND: Optic pathway gliomas (OPG) are the most common primary tumors of the visual pathways, and constitute 5% of all brain tumors in children. The aim of this study is to document our OPG patients.

INTRODUCTION: Not all low grade gliomas (LGG) will benefit from a carboplatin-based chemotherapy. A better understanding of factors
LG-36. DNA METHYLATION PROFILING OF LOW GRADE Astrocytomas using the Illumina 450K BeadChip reveals changes in genes involved in brain development and drug resistance

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Low grade astrocytomas are the most common central nervous system tumours in childhood. RAG gene fusions predominate in pilocytic astrocytomas (grade II), but these are not found in diffuse astrocytomas (grade III). This study examines 20 pilocytic and 10 diffuse astrocytomas, together with normal brain controls. The findings were validated in a larger tumour cohort, and compared with gene expression data. Unsupervised hierarchical clustering grouped these samples into tumour types and controls. Pilocytic astrocytomas located in the cerebral cortex did not group with those in the cerebellum, but grouped instead with the diffuse astrocytomas, all of which were located in the cerebral cortex. This may reflect site-specific regulatory mechanisms in the astrocytomas.

LG-37. IMP3 PROTEIN EXPRESSION IS A POTENTIAL INDEPENDENT PROGNOSTIC FACTOR IN PEDIATRIC PILOCYTIC AND PILOMYXOID Astrocytoma

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BACKGROUND: Pediatric pilocytic and pilomyxoid astrocytomas are biologically indolent and amenable to surgical cure if located in a favorable anatomical site. However, a significant number of children (> 55%) will eventually suffer from tumor progression. Although this tumor is unlikely to upgrade to a more aggressive astrocytoma, repeated recurrences and surgery can eventually result in devastating damage. Currently, there is no way to identify those patients whose tumors will progress.

Insulin-like growth factor-II messenger RNA (mRNA)-binding protein-3 (IMP3, IGF2BP3) has recently been identified as predictive of an unfavorable prognosis in a variety of non-CNS tumors. The aim of this study was to determine an expression of IMP3 and the prognostic value of its expression in pediatric pilocytic and pilomyxoid variant astrocytomas.

APPROACH: IMP3 protein expression was examined by immunohistochemistry in 81 primary tumors and was scored from 0 to 4 on a subjective scale. IMP3 mRNA expression was measured as part of whole-transcriptome analysis using Affymetrix U133plus2 GeneChips. RESULTS: Positive staining for IMP3 (score >2) was observed in 32% (26/81) of the tumors and correlated significantly with progression (p = 0.005). Potential confounding factors were addressed by multivariate analysis and IMP3 expression was identified as an independent prognostic factor for tumor progression. IMP3 mRNA expression correlated with protein expression, although a prognostic correlation was not seen with IMP3 mRNA in this smaller cohort of patient samples. IMP3 mRNA expression was 16-fold higher (p < 0.005) in pilomyxoid (n = 7) than pilocytic astrocytoma (n = 15) but this was not recapitulated at the protein level. CONCLUSIONS: IMP-3 protein expression warrants further evaluation as a predictor of poor prognosis in pediatric pilocytic and pilomyxoid astrocytomas.

LG-38. RAG GENE ABNORMALITIES DEFINE SUBSETS OF PEDIATRIC LOW-GRADE GLIOMAS AND GLIONEURONAL TUMORS

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Recent studies have highlighted RAG gene abnormalities as driver mutations in low-grade gliomas (LGGs) and glioneuronal tumors (GNTs). Their principal effect is upregulation of the MAPK pathway. KIAA1549-BRAF fusion genes dominate, and are strongly associated with pilocytic astrocytomas (PAs), particularly those in the posterior fossa. Here, we present data on the genomic landscape of pediatric LGGs and GNTs, focusing on abnormalities that disturb the MAPK pathway. LGGs and gangliogiomas (n = 177) were analyzed for KIAA1549-BRAF or SRGAP3-RAF1 fusion genes and BRAFV600E, KRAS or IDH1 mutations, using standard methodologies. Results were compared to clinicopathological data. RAG fusion genes were detected only in PAs, pilomyxoid astrocytomas and a single pilomyxoid glioma. Their prevalence among these tumors varied by anatomic site: spinal - 100%, posterior fossa - 93%, supratentorial - 44%. KIAA1549-BRAF exon15-exon9 and exon16-exon9 fusions were most prevalent. BRAFV600E mutations (n = 20) were confined to pilomyxoid astrocytomas (PAs), gangliogiomas (GGs), diffuse astrocytomas (DAs) and two supratentorial PAs (both negative for a RAG fusion gene). Tumors that did not harbor one of the assayed mechanisms for aberrant upregulation of the MAPK pathway were all supratentorial and, by histopathological type, were oligo/neural tumors (100%), DAs (87%), and
GLIOMAS

INTRODUCTION: Pediatric low-grade gliomas (LGGs) are among the most common central nervous system (CNS) tumors in pediatrics. Carcinoblast-vincristine combination therapy is commonly used for LGGs that are unresectable and to avoid radiation therapy (RT). Due to vincristine (VCR) toxicities, a carboplatin-only regimen would be desirable.

METHODS: Patient data was culled from the pediatric neuro-oncologic patient database. Eligible patients were followed at MSKCC and treated with carboplatin and vincristine per the Childrens Oncology Group protocol A9992. To eliminate the possibility of chemotherapy and in the results of this study, patients were censored if they had received any prior chemotherapy. Tumor response was assessed based on the criteria given in the COG A9992 protocol.

RESULTS: Patient data for 21 children with LGG on COG A9992 were collected. Nine children (43%) had their VCR dose reduced or discontinued because of neurotoxic effects. Observed VCR toxicities are reported in the chart above. The mean percent of total VCR dosage received in children with dose reduction/discontinuation was 55%. Patients who had VCR reduction/discontinuation had an average of 3.6 weeks during the entire 60 week regimen in comparison to patients without VCR dose alteration having treatment held an average of 11.1 weeks.

CONCLUSIONS: A weekly carboplatin-only regimen will provide survival rates that are not statistically different from the standard carboplatin-VCR treatment. Dose intensity during treatment did not contribute towards the EFS rate variation as treatment was held more in patients without VCR modification. Single-agent weekly carboplatin therapy should be further investigated as a treatment option for pediatric LGGs.

LG-39. WEEKLY CARBOPLATIN-ONLY OFFERS SIMILAR SURVIVAL TO VINCISTINE/CARBOPLATIN IN LOW-GRADE GLIOMAS

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INTRODUCTION: Pilocytic astrocytoma (PMA) is a rare variant of pilomyxoid astrocytoma (PMA). Compared to PA, PMA is more aggressive, has a higher rate of local recurrence, and often disseminates to the leptomeninges. Leptomeningeal gliomatosis is another rare but often intractable neoplasm. PMA presenting as leptomeningeal gliomatosis can be a therapeutic challenge, particularly in young children for whom many pediatric oncologists consider radiation therapy as a back up treatment. However, chemotherapy, usually considered a front-line treatment for low-grade tumors such as PMA, has little impact on leptomeningeal gliomatosis.

CASE REPORT: We report on a 5-year-old boy with an approximately 2-month history of progressively worsening loss of vision. Radiographic contrast revealed an enhanced mass within the optic nerve, an enhanced lesion in the leptomeninges, and diffusely scattered non-enhanced white-matter lesions in the craniospinal axis. Since imaging studies were consistent with a low-grade glioma of optic glioma, the patient was treated with a 10-week carboplatin and vincristine regimen without a biopsy. After completing induction and one maintenance cycle the patient went into a coma caused by an enlarged ventricle. An external ventricular drainage was inserted and a biopsy was performed through ventriculocytoclysis. Biopsied tissue was consistent with PMA. The patient was then treated with craniospinal irradiation (CSI) and concomitant temozolomide, a regimen to which he had a complete response. Two years after initial presentation the patient was disease free.

CONCLUSIONS: This report documents a rare, intractable tumor and provides evidence that radiation therapy, given as CSI, is effective as a treatment for leptomeningeal gliomatosis.

LG-40. SUCCESSFUL TREATMENT OF LEFTOMENINGEAL GLIOMATOSIS OF PILOMYXOID Astrocytoma AFTER FAILED TO FRONT-LINE CHEMOTHERAPY: A CASE REPORT

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INTRODUCTION: Pilocytic astrocytoma (PMA) is a rare variant of pilomyxoid astrocytoma (PA). Compared to PA, PMA is more aggressive, has a higher rate of local recurrence, and often disseminates to the leptomeninges. Leptomeningeal gliomatosis is another rare but often intractable neoplasm. PMA presenting as leptomeningeal gliomatosis can be a therapeutic challenge, particularly in young children for whom many pediatric oncologists consider radiation therapy as a back up treatment. However, chemotherapy, usually considered a front-line treatment for low-grade tumors such as PMA, has little impact on leptomeningeal gliomatosis.

CASE REPORT: We report on a 5-year-old boy with an approximately 2-month history of progressively worsening loss of vision. Radiographic contrast revealed an enhanced mass within the optic nerve, an enhanced lesion in the leptomeninges, and diffusely scattered non-enhanced white-matter lesions in the craniospinal axis. Since imaging studies were consistent with a low-grade glioma of optic glioma, the patient was treated with a 10-week carboplatin and vincristine regimen without a biopsy. After completing induction and one maintenance cycle the patient went into a coma caused by an enlarged ventricle. An external ventricular drainage was inserted and a biopsy was performed through ventriculocytoclysis. Biopsied tissue was consistent with PMA. The patient was then treated with craniospinal irradiation (CSI) and concomitant temozolomide, a regimen to which he had a complete response. Two years after initial presentation the patient was disease free.

CONCLUSIONS: This report documents a rare, intractable tumor and provides evidence that radiation therapy, given as CSI, is effective as a treatment for leptomeningeal gliomatosis.

LG-41. MicroRNA PROFILING OF PEDIATRIC PILOCYTIC ASTROCYTOMA REVEALS BIOLOGICALLY RELEVANT TARGETS

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BACKGROUND: Pilocytic astrocytoma is a WHO grade I glioma that occurs most commonly in children and young adults. Specific genetic alterations have been described in PA, but the pathogenesis remains poorly understood. MicroRNAs (miRNAs) are short single-stranded RNA molecules that function as post-transcriptional regulators. Altered miRNA expression has been shown to be implicated in multiple human cancers including brain tumors. Therefore we sought to study miRNA alterations in a clinically and genetically characterized cohort of PA.

METHODS: A total of 43 PA (median age 10 years) including 35 sporadic grade 1 PA, 4 neurofibromatosis type 1-associated PA, 4 PA with pilomyxoid features and 5 non-neoplastic brain controls were examined. KIAA1549:BRAC fusion status was assessed in most cases. Total RNA extracted from frozen tissue was hybridized to the Human miRNA Microarray V3 kit platform (Agilent). Expression of candidate miRNAs was validated by qRT-PCR using Taqman probes in a subset. Validation of predicted protein targets was performed on tissue microarrays by immunohistochemistry.

RESULTS: miR-206 was found to be significantly down-regulated (16.6 fold) in PA compared to non-neoplastic controls. The expression of predicted targets were further increased at the mRNA and protein levels in independent PA datasets, including PBX3 and METAP2.

CONCLUSIONS: Our study identified a unique PA miRNA expression profile compared with non-neoplastic brain tissue. These miRNAs may play a role in the pathogenesis of PA, and confirm the value of molecular profiling for identification of relevant protein targets in PA.

LG-42. CLINICAL SIGNIFICANCE OF AGE AND THE QUALITY OF THE RESPONSE TO TREATMENT IN CHILDREN WITH OPTIC PATHWAY GLIOMAS: A SINGLE INSTITUTION EXPERIENCE

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BACKGROUND: Optic pathway gliomas (OPGs) comprise about 5% of pediatric intracranial tumors, and present most frequently in the first 5 years of life. Although the survival rate of OPG patients is high, the majority of patients will experience tumor progression with a risk of long-term morbidity. Young age which has been identified as unfavorable prognostic factor of childhood OPGs in several reports with variable cut-offs. We attempted to assess the influence of age in a large institutional group of OPG patients.

METHODS: We reviewed the medical record of all OPG patients from 1980-2011. We divided the patients into 4 groups according to their age at diagnosis: group 1: 0-<18 months; 2: >18 <36 months; 3: >36 <60 months; 4: >60 months. The median follow up time was 9.96 years (0.4-19.2 years). RESULTS: 95/146 (65.0%) patients had neurofibromatosis-1 (NF-1), but their distribution was unequal, as only 4/21 (19%) were in group 1. 75/146 (51%) patients received treatment for tumor and/or clinical progression: 19/21(90%) in group 1; 22/33(62.9%) in group 2; 15/46 (32.6%) in group 3 and 19/44(43.2%) in group 4. 8 (38%), 3(9.6%), 2(4.3%) and 4 (9.3%) patients received 3 or more than 3 lines of treatment in each group. Overall, 9 patients were irradiated during the study period. 4 (9.44%) of them were <18 months old at the time of diagnosis. Four patients died, 3 were group1 and death was due to tumor progression. The 2 year progression-free survival in each respective group was 41.9%, 70.6%, 82.6% and 83.7%. CONCLUSIONS: Patients who were younger than 18 months of age have more aggressive OPG. The visual outcome and quality of life according to age at diagnosis is currently assessed.
INTRODUCTION: Tectal gliomas (TG) are low-grade astrocytomas with an indolent clinical course; rarely, they can be aggressive with rapid disease progression. Here, we present two cases of aggressive TG in children. PATIENTS: Patient #1, a 9-year-old female who presented with headaches and vomiting. Brain MRI revealed hydrocephalus and a tectal mass with a small area of enhancement and restricted diffusion. She underwent a biopsy and endoscopic third ventriculostomy (ETV) revealing low-grade glioma. Follow-up MRI three months later revealed increase in the previously-noted area of enhancement and necrosis, with increased choline-creatinine and a more prominent lactate peak on magnetic resonance spectroscopy (MRS) suggestive of a high-grade lesion. The patient was treated with focal irradiation and temozolomide; 18 months from diagnosis, the patient demonstrated rapid clinical deterioration and MRI revealed tumor progression with dissemination to the cerebellum with a metabolic profile typical for high-grade glioma; the patient expired a week later from disease progression. Patient #2 was 8 years old at diagnosis and presented with headaches and vomiting. Brain MRI demonstrated a non-enhancing left tectal mass with hydrocephalus. She underwent ETV but no biopsy, with resolution of symptoms. Four years after initial diagnosis, she developed rapid clinical and radiographic progression with MRI showing marked tumor enlargement with a new area of contrast enhancement and necrosis and significant increase in choline-creatinine on MRS suggestive of a high-grade glioma. The patient received focal irradiation with daily oral etoposide and carboplatin. Post-treatment MRI revealed a significant decrease in tumor size, presently with a new area of contrast enhancement and necrosis and significant increase in choline-creatinine on MRS suggestive of a high-grade glioma. The patient received focal irradiation with daily oral etoposide and carboplatin. Post-treatment MRI revealed a significant decrease in tumor size, presently stable on maintenance chemotherapy with temozolomide, irinotecan and bevacizumab. CONCLUSIONS: Although most TGs in children have an indolent behavior, a small number have the potential for an aggressive course including malignant transformation. Collaborative studies are warranted for risk-stratification of TGs to permit early detection and appropriate management of aggressive variants.

BACKGROUND: To report a rare malignant presentation on the optic pathway glioma (OPG) in children. The clinical course, treatment strategies, morbidity, and mortality were demonstrated in this series. PATIENTS AND METHODS: A series of 6 patients with malignant OPGs retrospectively followed in Taipei Veterans General Hospital from 1990 to 2013. Most patients had rapidly progressing visual loss along with visual field defect. The average age was 7.3 years old. The tumor was most often involving optic nerve in 4, optic chiasma in 4, optic tract in 4, and hypothalamus in 2. There are 3 patients had obstructive hydrocephalus and needs VP shunt for CSF diversion. Gross total resection of tumor was difficult to achieve in these patients. All the specimen was sent for further analysis. RESULTS: Anaplastic features (Grade III) were found in 5 cases, and one specimen was defined as glioblastoma (Grade IV). Five patients received adjuvant radiotherapy and chemotherapy (Temodol, cisplatin, vinblastin, and etoposide). Some of the patients can be controlled in a short of periods (2, 3, 8 years in three patients). Local recurrence or diffuse leptomeningeal seeding were found within 2-3 years, accompanying with visual deterioration and consciousness disturbance. CONCLUSIONS: The outcome of malignant OPG was usually fatal in reported cases. New treatment paradigm with concomitant TMZ radiotherapy (TMZ + RT) and adjuvant TMZ for GBM may improve the outcome of malignant OPG in children for only a short period of time, even on the ones with methylated MGMT promoter.

BACKGROUND: To report two cases of malignant optic pathway gliomas (OPG) in children. OPG occurs in children aged the first 20 years of age with sporadic suprasellar OPG were included. Potential prognostic factors studied included age, gender, anatomical site, chemotherapy (7/19), combined surgery/chemotherapy (3/19) and palliative care (2/19). 5/7 of patients with optic pathway gliomas (OPG) and 6/7 of patients with WHO grade I histology responded to salvage treatment, whereas only 1/4 of thalamic gliomas patients did respond. At the last follow-up, 11 patients were alive; including 7/10 patients who received salvage chemotherapy. Seven patients died of tumor progression. Five-year DFS and OS after radiotherapy failure was 53.8% and 59.4% respectively, with a median follow-up time 2.28 years (range 0.19-19.33 years).
LG-47. PILOMYXOID ASTROCYTOMAS: REVIEW OF CLINICOPATHOLOGICAL FEATURES IN A SERIES OF TWENTY CASES

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INTRODUCTION: Pilomyxoid astrocytomas (PMA), are low grade WHO grade II astrocytic tumours. MATERIALS AND METHODS: 22 cases were retrieved from the department files of last eight years. RESULTS: 2 were excluded due to lack of adequate paraffin blocks. 20 formed the study sample.14 males and six females; Age distribution ≤6 yrs; 8, 7-14yrs; 7, 15-18yrs and ≥18yrs. Prominent (n = 10 cases) were in suprasellar and others are posterior fossa: 6, 3rd ventricle - 2, and hemispheric. -2. Radiology was available for 19 cases and showed well defined circumscribed. Except one residual did not calcify (heterogenous:11, homogenous:5 and rim:2). Most of them (n = 13) were solid and six showed cystic change. All of them showed oval to elongated oval shaped tumour cells with atelectic focus of conspicuous myoid fibrillary matrix background. Focal perivascular radial condensation of tumour cells was noted only in 8 cases. Microcystic change and calcification was noted in 5 and 3 cases respectively. Biphasic architecture, Rosenthal fibres and eosinophilic granular bodies were not seen. Occasional mitotic ac-

LG-48. LONG-TERM OUTCOME FOR PEDIATRIC PATIENTS WITH DYSSEMBRYOPLASTIC NEUROEPITHELIAL TUMORS

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BACKGROUND: Dysembryoplastic neuroepithelial tumor (DNET) is a low-grade glioneuronal pediatric brain tumor. Evidence suggests that children with DNET may be at risk of recurrence and malignant transformation. We reviewed clinicoanatomical, radiographic, and pathologic characteristics of 54 children with DNET to identify prognostic features. METHODS: We retrospectively reviewed all patients diagnosed with a DNET at the Hospital for Sick Children (Toronto, Canada) and Cincinnati Children’s Hospital Medical Center from 1987 to 2011. Data analyzed included demographics, clinicopathological features, imaging features, pathology, therapy, and outcome. Pathologic assessment included vascular proliferation, necrosis, MIB-I index, mitoses and chromosomal LOH. Radiological features included tumor size/location, MR signal characteristics, and presence of calcification, dural enhancement. Histopathological analysis and radiographic features will be performed to identify prognosticators for recurrence. RESULTS: Of 54 patients, 59% were male and 93% presented with seizures, most commonly focal (81%). Time from diagnosis to first surgery was noted in 14 cases. Follow-up data (6mon:3, 1-3% in 9 cases, 3-4% in 4 cases, 4-6% in 6 and 6-8% in 1. Gross total re-

LG-49. WHOLE CHROMOSOMAL INSTABILITY CHARACTERIZES A LARGE SUBSET OF ADULT PILOCYTIC ASTROCYTOMA AND CORRELATES WITH WORSE PROGRESSION-FREE SURVIVAL

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Sporadic pilocytic astrocytoma (PA) is a WHO Grade I astrocytoma and the most common primary brain tumour in children. Genetic aberrations in the MAPK pathway have been reported in the vast majority of sporadic PA, with a frequent p53 mutation. However, in adult PA, a significant proportion (34%) of patients present with a KIAA1549-BRAF fusion, which is associated with worse progression-free survival. We performed an IRB approved retrospective review of all adult patients with PA who were 21 years or older at the time of diagnosis and had at least 2 years of follow up. In total, 31 patients were included in the study. Genomic characterization was performed using whole-exome sequencing in 20 cases, and array comparative genomic hybridization in 11 cases. We identified whole-chromosomal gain in 6/31 cases (19%) and whole-chromosomal loss in 6/31 cases (19%). No cases presented with both abnormalities. In addition, we identified copy number loss of 1p and 19q in 1 case each and 1p/19q LOH in 6 cases. The two cases of 1p deletion and 1p/19q LOH shared recurrent copy number loss of 1p and 19q, and had the highest levels of MIB-1 labeling index (44%). The two cases with 19q LOH had lower levels of MIB-1 labeling index (11% and 4%). No cases had local or systemic therapies. At the last follow-up, all 31 cases were alive, with an overall 2-year progression-free survival of 84%. Median overall survival was 2.5 years (range, 1.5-8 years). In conclusion, whole-chromosomal instability is a common genetic aberration in adult PA and is associated with worse progression-free survival.
NF1 who were treated with vincristine for low grade glioma between 1994-2011 and a subset of age- and gender-matched non-NF1 patients. Data collection included indication for treatment, duration of treatment, cumulative vincristine dose, number of omitted and reduced vincristine doses, and signs/symptoms of neurotoxicity. RESULTS: 18 patients were identified with NF1 (56% male); median age at treatment with vincristine was 5.9 years and median duration of treatment was 1.1 years. The comparison population included 18 patients without NF1 (50% male); median age at treatment was 4.3 years and median duration was 1.2 years. Gender, age at treatment, and duration of treatment were not statistically different (p = .74, p = .16 and p = .29, respectively). Six patients without NF1 (33%) received modified doses of vincristine due to CIPN compared to 15 patients with NF1 (83%, p = .01). Toxicity included: leg pain, jaw pain, constipation, irritability, ptosis, other cranial nerve impairment, and distal weakness. CONCLUSION: These results support the hypothesis that children with NF1 are at increased risk to develop CIPN. Further investigation of the pathophysologic contribution of neurofibromin haploinsufficiency in risk for chemotoxicity is warranted.