NEUROONCOLOGY & NEURORADIOLOGY

FP112

EVEROLIMUS FOR SUBEPENDYMAL GIANT CELL ASTROCYTOMA (SEGA) ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX (TSC): EXIST-1 LONG-TERM EFFICACY AND SAFETY RESULTS

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Introduction: EXIST-1 (NCT00789828), a randomized, double blind, phase 3 trial, demonstrated that everolimus, an mTOR inhibitor, was superior to placebo for reducing SEGA volume in patients with TSC. Long-term safety and efficacy of everolimus were examined using data available 11-January-2013.

Methods: Patients (median age, 9.5 years [range, 0.8-26.6 years]) received 4.5mg/m^2/day oral everolimus (n=78; titrated to a target trough 5-15ng/mL) or placebo (n=39). SEGA response rate (primary endpoint) was defined as proportion of patients with ≥50% reduction in sum of volumes of all target SEGA (≥1 SEGA ≥1 cm in longest diameter) versus baseline. Adverse events (AEs) were monitored at every visit.

Results: Everolimus was superior to placebo for SEGA response rate (34.6% vs 0.0%; *P* 0.0001; original cut-off, 02-March-2011). Following positive results for original cut-off, placebo patients were offered open-label everolimus in the study's extension phase. As of 11-January-2013, 111 patients received ≥1 dose of everolimus and were included in this extension analysis. Median treatment duration of everolimus was 29.3 months and SEGA response rate was 48.6% (95% confidence interval [CI], 39.0-58.3%). As of 11-January-2013, median time to SEGA progression was not reached; however, SEGA progressions were observed for 9 (8.1%) patients. Most AEs continued to be grade 1 or 2. The most frequent serious adverse events occurring in more than 3% of patients were pneumonia (10.8%), pyrexia (4.5%), gastroenteritis (3.6%), and convulsion (3.6%).

Conclusion: Everolimus continued to reduce SEGA volume with no new safety concerns.

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SAFETY OF EVEROLIMUS IN PATIENTS <3 YEARS OLD WITH SUBEPENDYMAL GIANT CELL ASTROCYTOMA (SEGA) ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX (TSC): SUBGROUP RESULTS FROM THE PLACEBO-CONTROLLED, PHASE 3 TRIAL EXIST-1

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Introduction: Clinical manifestations of TSC increase over time and may begin in utero. Everolimus, an mTOR inhibitor, was superior to placebo for reducing SEGA volume in the EXIST-1 trial (NCT00789828; median age, 9.5 years; response rate: everolimus, 35% vs placebo, 0.0%; *P<0.0001*; original cut-off, 02-March-2011). The safety of everolimus among patients 3 years old was evaluated in the open-label, long-term extension phase of EXIST-1 (28.3 months' follow-up [range, 1.9-38.8 months]; cut-off, 11-January-2013).

Methods: Patients with ≥1 SEGA (≥1 cm in longest diameter) received 4.5 mg/m^2/day oral everolimus (target trough, 5-15 ng/mL). Adverse events (AEs) were graded according to NCI-Common Terminology Criteria for Adverse Events version 3.0. We report safety data for patients 3 years old at the start of everolimus treatment (n=18; 12 males, 6 females).

Results: As of 11-January-2013, median duration of everolimus exposure in patients 3 years old at the start of treatment was 31.1 months (range, 11.5-39.0 months). The incidence of serious AEs was 50.0% (n=9); incidence of grade 3-4 AEs was 77.8% (n=14). Incidence of AEs requiring dose interruption and/or reduction was 94.4% (n=17). Most common AEs (occurring in 40%) were stomatitis (66.7%), cough (44.4%), pharyngitis (44.4%), and pyrexia (44.4%).

Conclusion: No new safety concerns were identified among patients <3 years old treated with everolimus. The small sample size in this subpopulation limits interpretation of the results.

FP114

POSTERIOR FOSSA SYNDROME AND MUTISM IN CHILDREN AFTER CEREBELLAR TUMOR SURGERY

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Introduction: Posterior fossa syndrome (PFS) is characterized by neurobehavioral symptoms, such as eating dysfunction, mood disorders, regressive behaviour, apathy, eyelid apraxia, lack of bowel and bladder control, and decreased spontaneous initiation of voluntary activities. PFS and mutism have been documented in approximately 8-29% of children operated for cerebellar tumor. The aim of this study was to describe the prevalence, clinical features, and outcome in patients with PFS and/or mutism.

Methods: Charts and neuroimages of 178 patients who underwent cerebellar tumor surgery seen between 2000-2009 were reviewed. Inclusion criteria: Patients with PFS and/or mutism and normal development before tumour surgery. Results: Thirteen patients (7.3%), 10 males, were included. Mean age at surgery was 6.9 years (range, 1.7-10 years). Primary tumour location: Vermis+hemisphere (56%), cerebellar hemisphere (31%), and vermis (23%). Medulloblastoma, pilocytic astrocytoma, desmoplastic medulloblastoma, and astrocytoma were diagnosed in three patients each, and ependymoma in one. Preoperatively, all had hydrocephalus. Tumor resection was total in 54% and partial in 46%. Post-surgical mutism was observed in 11 (85%) with a mean duration of 54 days (range, 19-130 days) and PFS in nine (associated with mutism in seven). Mean follow-up was 4.6 years. Three patients died because of tumor. Mutism was followed by dysarthria in all. The neurobehavioral symptoms resolved in all cases, but four children required special school.

Conclusion: PFS and mutism are a dramatic clinical event following cerebellar surgery. Although neurobehavioral symptoms and mutism resolved, the neurocognitive outcome was poor.

FP115

GLIOMATOSISCERIBRI IN CHILDHOOD – CASE REPORT

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Introduction: Gliomatosis Cerebri (GC) is a rare neoplastic situation in childhood, characterized by diffuse infiltration of glial cells in the Central Nervous System (CNS), with a wide variety of presentations and an unfavourable outcome.

Case report: An 11-years-old boy began with behavioral alterations, amnesic aphasia as well as right hemiplegia. Brain MRI showed diffuse infiltrative lesions involving both hemispheres. These lesions, identified largely on the white matter of the left hemisphere, encompassed frontal, temporal and parietal lobes, extending into basal ganglia, and mesencephalon, as well as bilateral thalami and white matter of the contralateral hemisphere, were hyperintense on T2 and flair sequences. The spectroscopy analysis showed increased peak of mioinositol, reduction of peak of N-acetyl-Aspartate, and some areas with a slight increase in the peak of choline. Brain biopsy evidenced grade 3 astrocytoma. He received combined treatment with temodal and radiotherapy.

Discussion: In GC, different portions of the CNS are diffusely intermixed by neoplastic cells with preservation of anatomic architecture. It is not a unique cytogenetic entity, and the evolution depends on the histologic grade. The disease has a bimodal distribution, with peaks in the second and fifth decades of life. Usually, seizures are the first symptom, followed by hemiparesis, lethargy, other mental status alterations and visual loss. The MRI images are unspecific, and differential diagnosis includes ischemia, multiple sclerosis, encephalitis and leukodistrophy.

Brain biopsy is extremely helpful to diagnosis confirmation. Treatment is based on chemotherapy.

FP116

SERUM ALPHA-TOCOPHEROL, VITAMIN B12 AND FOLATE LEVELS IN CHILDHOOD ALL (ACUTE LYMPHOBLASTIC LEUKEMIA) SURVIVORS WITH AND WITHOUT NEUROPATHY

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Introduction: Children with Acute Lymphoblastic Leukemia are often malnourished and may have multiple nutritional deficiencies. This study aimed to assess the prevalence of vitamin E, Vitamin B12 and folate deficiency in childhood Acute Lymphoblastic Leukemia (ALL) survivors who had received vincristine-based chemotherapy with and without neuropathy.

Methods: This cross-sectional study was carried out in a tertiary care centre of north India from October 2011 to July 2012. Children with Acute lymphoblastic leukemia aged between 5 to 18 years in first continuous remission within 3 years of completion of vincristine-based chemotherapy were enrolled. After informed consent, the enrolled children underwent detailed clinical examination and review of their clinic files. This was followed by detailed nerve conduction studies. Subsequently, 4 ml of blood sample was withdrawn and analysed for serum α tocopherol, serum cholesterol and triglycerides, serum vitamin B12 and folate levels.

Results: 80 children were studied. The mean age at the time of evaluation was 11.2 years (SD: 4; Range: 1.5-16 years). The neuropathy was seen in 27 (33.75%) children electrophysiologically. None of the children had vitamin E deficiency. However, the alpha-tocopherol/(cholesterol + triglyceride) ratio was significantly lower in children with neuropathy (p=0.05). The prevalence of folate (p=0.48) and vitamin B12 (p=0.21) deficiency in children with and without neuropathy was not significantly different.

Conclusions: The prevalence of deficiencies of these micronutrients was not significantly different in children with or without neuropathy. However, larger studies are warranted to study the contribution of micronutrient deficiency towards development of neuropathy in ALL survivors.

FP117

SPECTRUM OF NEUROLOGICAL COMPLICATIONS IN CHILDHOOD MALIGNANCIES-A STUDY FROM INDIA

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Aim: To describe neurological complications in children with cancer Study period- November 2008 - Aug 2013

Methods: Neurological problem as presenting feature or part of therapy related complications in childhood malignancies, identified and reviewed. Exclusion-Pre existing neurological problems, with CNS tumours& post chemotherapy cognitive dysfunctions excluded. Type of Study**:** prospective (3 years) and Retrospective (1 and half yrs.)

Results: 38/248 children, 3 months to 15 years of age reviewed. Acute lymphoblastic leukemia (ALL) 17/38, neuroblastoma (NBL) 9/38. Four of 9 had Opsoclonus Myoclonus syndrome. Neurological problems with Ewings /PNET seen in 4. Histiocytic disorder with CNS deposits 3. Two were Acute myeloid leukaemia. Tumour related neurological problems: seen in 23, remaining 15 therapy related. 19 /23 directly related to tumour, 4/23 were paraneoplastic as Opsoclonus myoclonus secondary toneuroblastoma. Cord compression-9, (NBL-3, Ewings/PNET-4, Germ cell tumor-1, RMS-1). Five presented with seizures (ALL-3, AML-1, Histocytosis-1), Encephalopathy with seizure in one with histiocytosis. Two had facial nerve palsy with tumour infiltration (one AML/one DLBL). One Ptosis (with intracranial neuroblastoma extension) and 1 primary HLH presented with headache and vomiting secondary to CNS deposits. Therapy related problems seen 15 cases. Stroke like presentations seen in children (Methotrexate induced). Seizures post methotrexate-4 (MTX)/cortical venous thrombosis therapy in 1(post PEG Asparganise). One had ventriculitis while on Induction. One child had post MTX chemical meningitis. One had Posterior reversible Encephalopathy syndrome secondary to hypertension (Steroid).

Conclusion: Early recognition of neurological complication either disease or treatment related is essential to control mortality & morbidity. Awareness of different treatment /disease related neurological manifestations essential

FP118

WHITE MATTER MICROSTRUCTURAL INTEGRITY IN SYNDROMIC AND IDIOPATHIC AUTISM

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Introduction: MRI Diffusion Tensor Imaging (DTI) is used to assess the microstructural integrity of white matter. Subjects with both idiopathic autism spectrum disorder (ASD) and syndromic autism, such as in tuberous sclerosis complex (TSC), have altered diffusion in white matter pathways, but no study has investigated if diffusion parameters are similar across syndromic and idiopathic ASD. We hypothesize that diffusion abnormalities are common in autism regardless of its aetiology and will use a four-point comparison between subjects with idiopathic autism, TSC with ASD, TSC without ASD, and controls to determine if diffusion values in the corpus callosum (CC) are similar across subjects with ASD.

Methods: DTI was performed in four age-matched (2.7-18.9yo) groups: 14 with idiopathic ASD, 13 with TSC and ASD, 13 with TSC without ASD, and 12 controls. Tractography of the CC was performed and fractional anisotropy (FA) and mean diffusivity (MD) were calculated for each subject. To distinguish effects related to ASD from those related to TSC, a two-way analysis of covariance (ANCOVA) will be applied, using age as a covariate.

Results: It is expected that subjects with TSC and ASD will have statistically similar FA and MD values in the CC as subjects with idiopathic autism and that these values will differ from both TSC subjects without ASD and controls.

Discussion: The results of this study will better elucidate if microstructural changes measurable on MRI correlate with the autism phenotype regardless of etiology; such results would suggest DTI imaging could be a biomarker for ASD.

FP119

MICROSTRUCTURAL ABNORMALITIES OF THE SUPRATENTORIAL WHITE MATTER TRACTS ON BRAIN MRI IN X-LINKED MCT8 DEFICIENCY: IMPLICATIONS FOR EARLIER DIAGNOSIS AND TREATMENTS.

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Introduction: Loss-of-function mutations in the X-linked Monocarboxylate Transporter 8 (MCT8) gene result in thyroid hormone cell transporter deficiency. Affected children present with moderate-severe psychomotor disability, hypotonia, and dystonic movements. Previously published brain MRI data suggests that these children have abnormal myelination in the absence of significant structural abnormalities. In light of this data, we hypothesized that MCT8 deficiency affects the structural development of complex cortical networks— specifically regional subcortical connections—which can be assessed with MRI.

Methods: We reviewed fourteen brain MRIs from a multinational cohort of patients with MCT8 mutations (n=6), aged 8 months to 7 years. We obtained longitudinal conventional MRI data in 5 patients and longitudinal diffusion tensor imaging (DTI) in 2 patients to evaluate for regional micro-structural abnormalities.

Results: T1- and T2-weighted imaging revealed delayed myelination at 8 months of age with slow improvement over time. By 3-to-5 years, the supratentorial white matter tracts showed patchy high T2 signal intensity that predominantly involved the peritrigonal regions and subcortical U-fibers. DTI demonstrated multiple foci of reduced fractional anisotropy in the supratentorial white matter, suggesting the presence of subtle microstructural abnormalities.

Conclusion/Discussion: The white matter tract abnormalities seen on brain MRI likely reflect disruptions in cortical-subcortical connectivity. These disruptions may explain certain aspects of the MCT8 deficiency phenotype and may guide future therapy selection.

FP120

ATYPICAL CASE OF A HSV-1 MENINGOENCEPHALITIS (HSE) INVOLVING CORPUS STRIATUM

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HSE involvement commonly occurs in the regions of inferomedial temporal lobe, inferior frontal lobe and insular cortex. We present a case of a meningoencephalitis with Corpus Striatum involvement that, to our knowledge, has not been reported in the literature previously, which was proved to be HSV-1 by PCR, and it can be considered as an atypical involvement for HSE.

Case Report: A 17-month-old female patient was brought with complaints of fever, lethargy and seizures. Brain MRI findings were suggestive of encephalomalacia with cystic changes detected in bilateral frontal, left temporal and left parietal lobes also bilateral medial parts of the thalamus, and also, increased T1 signal intensity compatible with laminar necrosis was detected in the cortex. In T2 sequences, increased signal intensity was observed at the head of the left caudate nucleus and the superior part of the lentiform nucleus, bilateral posterior frontal and parietal, and left temporal deep white matter.

Discussion: In most cases, treatment is started based on possible MRI findings before PCR results are obtained. In literature, have been reported for white matter, brain stem, thalamus and basal ganglia. When there is no lesion in commonly involved regions of the brain, clinicians may have the tendency to ignore the diagnosis of HSV. We find it valuable to present this case to point out that HSV-1 may involve different regions of the brain other than classical involvements, so HSV should be kept in mind as well in such cases.

FP121

NOVEL FINDINGS WITH SUSCEPTIBILITY-WEIGHTED IMAGING IN ACUTE-STAGE PAEDIATRIC CONVULSIVE DISORDERS

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Aim: The purpose of this study was to describe the clinical use of acute-stage susceptibility-weighted imaging (SWI) in children with prolonged convulsive disorders.

Methods: We enrolled 11 children (5 boys and 6 girls; age range, 0–7 years; average age, 3.7 years) with prolonged convulsive disorders who had undergone SWI within 2 h after their seizures had terminated (the acute-stage group), and 10 control children (7 boys and 3 girls; age range, 0–15 years; average age, 6.4 years) with various conditions who had undergone SWI for reasons other than acute-stage convulsive disorders. Cerebral venous vasculatures between the groups were compared. The acute-stage SWI group was further divided into two groups: those who showed focal prominence of venous vasculature (focal group) and those who showed generalized prominence of venous vasculature (generalized group). Venous blood gases during seizure activity were compared between these two groups.

Results: All patients in the acute-stage SWI group showed prominence of cerebral venous vasculature compared to none the control group. Five patients (2 boys and 3 girls; age range, 0–7 years; average age, 4.7 years) were assigned to the focal group and six patients (3 boys and 3 girls; age range, 1–6 years; average age, 2.9 years) to the generalized group. Respiratory compromise during seizure activity was more severe in the focal group than in the generalized group. The areas of venous prominence in the focal group were consistent with the electroencephalographic findings and had resolved completely in all patients.

Conclusion: This is the first study to demonstrate that acute-stage SWI may be a useful alternative method for differentiating focal seizures from generalized seizures in children with prolonged convulsive disorders.

FP122

CONVENTIONAL MAGNETIC RESONANCE IMAGING IN THE DIFFERENTIATION BETWEEN HIGH AND LOW-GRADE BRAIN TUMOURS IN PAEDIATRIC PATIENTS

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Aim: It has been described that hyperintensity in diffusion weighted imaging (DWI) correlates with high-grade tumours, and high signal-intensity in T2-weighted (T2w) images identifies low-grade tumours. We aimed to investigate the potential of routine conventional MRI sequences, such as DWI and T2-w, to pre-operatively distinguish between low-grade and high-grade brain tumours in paediatric patients.

MATERIAL AND METHODS: Two raters, blinded to the histological diagnosis, rated the aspect and signal intensity of MR images (T2w and DWI) from 37 children with newly diagnosed brain tumours. Histological diagnoses included 18 low-grade and 19 high-grade brain tumours.

RESULTS: The inter-rater agreement was 81-95%. High-grade tumours were never hypointense on DWI and low-grade tumours were usually hyperintense on T2w. Specificity was 100% for low-grade tumours and 90% for high-grade tumours. About 95% of the high-grade tumours and about 70% of the low-grade tumours were correctly diagnosed.

CONCLUSION: The combination of general morphological aspect of the tumours and signals on T2-w and DWI yield a high accuracy of pre-operative differentiation between low-grade and high-grade paediatric tumours.

FP123

EVALUATION OF THE NERVE CONDUCTION STUDIES AND AUTONOMIC FUNCTIONS IN PATIENTS WITH AGENESIS OF CORPUS CALLOSUM

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Aim: To evaluate the electrophysiological findings of patients with agenesis of corpus callosum. Material and

Methods: Children with agenesis of corpus callosum were included in the study. All patients were evaluated with electrophysiological studies and results were compared with age and sex matched healthy control group.

Results: A total of 11 patients with total agenesis of corpus callosum were enrolled in the study. The mean age of the patients was 2.99±2.06 years (range, 0.8 ±7.0 years). There were not significant differences between the patients and control group according to the valsalva ratio, RRIV during deep breathing, SSR latency (hand), SSR amplitude (hand), SSR latency (foot), SSR amplitude (foot) and 30/15 ratio.

Conclusion: although clinical or subclinical autonomic dysfunctions appear to be more prevalent in some syndromic patients with agenesis of CC, we did not detect any significant differences in patients with agenesis of CC and healthy control group.