METABOLIC DISORDERS

FP124

INSIGHTS INTO THERAPEUTIC MECHANISMS OF L-ARGININE THERAPY IN MELAS SYNDROME USING EXERCISE TESTING WITH CYCLE ERGOMETRY AND 31P-MRS OF MUSCLE

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Background: MELAS syndrome is associated with myopathy and exercise intolerance in addition to stroke-like episodes (SLEs). Recent work has demonstrated a beneficial effect of L-arginine therapy for treatment and prevention of SLEs. The purpose of this study was to evaluate the effects of arginine supplementation on muscle metabolism in vivo in patients with MELAS syndrome in an attempt to better understand the treatment effects of arginine.

Methods: We enrolled 3 siblings with MELAS syndrome and 4 controls. We employed case control methodology for comparison of baseline exercise parameters on 31P-MRS of muscle and graded cycle ergometry. We used a clinical trial study design to assess response of these parameters to single dose and 6 week steady-state L-arginine.

Results: 31P MRS of muscle: At baseline, phosphocreatine (PCr) levels were elevated in MELAS subjects (p=0.05), ATP levels were decreased (p=0.01), and PCr/ATP ratio was elevated (p=0.01). The concentration of magnesium was lower in MELAS subjects (p=0.0001). Following L-arginine therapy, MELAS subjects demonstrated increased Pi/PCr with exercise (p=0.01 to 0.02), suggesting increased work capacity. One subject showed an extraordinary improvement in phosphocreatine recovery. Graded cycle ergometry: At baseline, mean percentage of VO2 max reached during exercise was lower in MELAS subjects (p=0.04). L-arginine therapy increased the percentage of maximum work at anaerobic threshold (p=0.037).

Conclusions: L-arginine supplementation produces a benefit in muscle metabolism in MELAS syndrome based on laboratory exercise testing. The mechanisms underlying these improvements are not yet elucidated, and may include improved bioenergetics and/or improved perfusion.

FP125

METHYLMALONIC ACIDEMIA: DIAGNOSIS AND LONG-TERM OUTCOME

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Introduction: Methylmalonic acidemias (MMA) are a heterogeneous group of inborn errors of branched-chain amino acids and of other propiogenic substrates metabolism, which are characterized by the accumulation of methylmalonic acid in many body fluids. The disease is caused by a defect of the enzyme methylmalonil-CoA mutase or by one of the defects in the metabolism of its cofactor, cobalamin (B12). This study aims to describe the evolution of 13 patients with MMA in Brazil, with emphasis on long-term outcome.

Methods: Retrospective observational study was performed in Neurometabolic Diseases outpatient of HCFMUSP Pediatric Neurology Department, assessing demographics features, age at diagnosis, clinical manifestations, exams results, treatment and complications.

Results: The mean follow-up time was 4 years (5m-12y). Median age at diagnosis was 25 months, which was 12 months for B12 non responsive forms and 31 months for responsive forms. Recurrent vomiting were present in 92% of the sample; hypotonia and development delay in 100% of vitamin B12 non responders and combined with homocystinuria forms. The median values of plasma methylmalonic acid was 464,5 in vitamin B12 responders patients, 1218,9 in vitamin B12 non responders and 1337 in combined with homocystinuria forms.

Conclusion/Discussion: The diagnosis in done lazily in Brazil. The vitamin B12 non-responders patients showed earlier onset of symptoms. In non-responders and combined with homocystinuria cases, development delay was more frequent than in cobalamin responders.

FP126

SUBACUTE COMBINED SCLEROSIS OF THE SPINAL CORD AFTER NECROTIZING ENTEROCOLITIS AND ILEAL RESECTION: A FORGOTTEN LINK

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This study aims to inform pediatricians and neonatologists on the existence of important nutritional deficits with clinical and subclinical manifestations in the child undergoing ileal resection in the neonatal period, which customarily arrive in outpatient pediatric neurologic services. Necrotizing enterocolitis (NEC) is a serious disorder affecting 1% to 5% of infants admitted to newborn intensive care nurseries. Surgical intervention to remove necrotic bowel is frequently required, and has particular significance because of the unique absorptive capacity of the ileum for fats, bile salts, and vitamin B12. The long-term effects of neonatal ileal resection on vitamin B12 absorption in later life are unknown. Vitamin B12 deficiency in children may potentially lead to anemia, neurologic abnormalities, and developmental delay. However, these signs may not manifest themselves for several years. The central nervous system manifestations may not be easily recognized in these former high-risk infants, and we thought that identification of a treatable condition, which could affect development, was important. There is a paucity of follow-up information on children who have undergone extensive ileal resection in the new- born period as a consequence of NEC. We emphasize the mandatory follow-up monitoring and evaluation for vitamin B12 deficiency of all patients who have undergone ileal resection for NEC. Further investigation into the use of serum homocysteine and methylmalonic acid as markers of asymptomatic vitamin B12 deficiency in children is warranted.

FP127

COENZYME Q10 DEFICIENCY: CLINICAL AND BIOCHEMICAL CHARACTERIZATION

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Introduction: Coenzyme Q10 (CoQ10) deficiency is a mitochondrial disorder with clinical and genetic heterogeneous presentations. Encephalomyopathy with recurrent myoglobinuria, severe infantile multisystemic disease, cerebellar ataxia, isolated myopathy and nephrotic syndrome are the main phenotypes described. The aim of this study is to identify patients with suspected CoQ10 deficiency and perform their clinical and biochemical characterization.

Methods: Twenty suspected patients between 0-10 years old were selected and submitted to clinical and laboratorial investigation. Fibroblast cell lines acquired from skin biopsies were submitted to chromatografic analysis and the Ultimate 3000 High Performance Liquid Chromatography measured CoQ10 levels. Mitochondrial redox state and enzyme activity from complexes I+III were analysed.

Results: Eleven patients (55%) had low CoQ10 concentrations. Two patients had isolated myopathy and showed 76% and 65% of CoQ10 residual content. Two patients had Leigh Syndrome and showed 60% and 98% of CoQ10 residual content. One patient had atypical clinical symptoms and 82% of CoQ10 residual content. Six patients had cerebellar ataxia and variable CoQ10 residual content, ranging from 52% to 92%. A significant increase in fibroblast levels of reactive oxygen species (ROS) was observed in 8 patients, suggesting bioenergetic deficiency.

Discussion: heterogeneity in CoQ10 content and ROS production observed in our population might be directly related to differences in clinical presentation and mutations between patients.

Cconclusion: characterization of CoQ10 deficiencies with clinical and biochemical features may help us understand and improve diagnosis. Once it is a treatable condition, early detection may change prognosis.

FP128

MELAS SYNDROME IS ASSOCIATED WITH IMPAIRED CEREBROVASCULAR REACTIVITY AND CEREBRAL HYPERPERFUSION IN BETWEEN STROKE-LIKE EPISODES

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Background: Stroke-like episodes constitute a major source of morbidity and mortality in MELAS syndrome. The pathophysiology of these episodes is incompletely understood, but is presumed to involve both direct neuronal injury and functional angiopathy as a result of mitochondrial energy failure. We performed a case control study using Blood Oxygen Level Dependent (BOLD) fMRI to evaluate baseline cerebral blood flow (CBF) and arterial cerebrovascular reactivity (CVR).

Methods: We enrolled 3 siblings with MELAS syndrome (A3243G tRNA leu) with varying percentages of mutant mtDNA and 4 healthy age and gender-matched controls. CBF was calculated using arterial spin labelling methodology. For CVR studies, subjects were fitted with an air-tight sequential gas delivery mask with gas delivery controlled using the RepirAct sequencer. Subjects were given a series of four CO2 challenges where PaCO2 was raised 10 mmHg above their baseline with PaO2 maintained at 100 mmHg.

Results: MELAS subjects demonstrated increased CBF and decreased CVR compared to controls, and the degree of abnormality correlated with disease severity and percentage of mutant mtDNA in blood. On regional analysis, mean CVR was reduced to a greater degree in the frontal compared to the occipital cortices.

Discussion: Patients with MELAS syndrome have impaired CVR and cerebral hyperperfusion in between stroke-like episodes, lending credence to a vascular and/or hemodynamic contribution to the latter. CVR and CBF may serve as prognostic markers to stratify risk for stroke-like episodes.

FP129

WHITE MATTER DISORDERS IN A SERIES OF 150 PATIENTS WITH METABOLIC DISEASE

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Introduction. The secondary disturbances of the white matter (WM) is caused by various diseases, like metabolic disorders, causing myelin detention or destruction.

Objectives. Identifying WM disturbances and describe the neuro-radiologic findings in patients with metabolic diseases diagnosed in our center.

Method. Descriptive study. Review patient´s clinical records and neuroimaging.

Results. 150 patients studied. 88 with WM disturbances. 4/6 PKU showed periventricular hypomyelination. 3/3 maple syrup urine disease with posterior fossa swelling. 15/150 Organic Acidemia; 11/11 Glutaric Acidemia type I with extensive involvement of WM, basal ganglia and fronto-temporal atrophy. 49/150 Lysosomal disorders; 11/49 lipofuscinosis with periventricular WM hyperintensity and cerebellar atrophy; 22/49 mucopolysaccharidosis, 8/11 type II showed periventricular WM and perivascular spaces involvement and diffuse atrophy. 8/49 Gangliosidosis; 3/3 type I showed periventricular WM involvement and 5/5 type II with symmetrical WM involvement and caudate, lenticular and thalamus hypointensity; 4/49 metachromatic leukodystrophy showed "tigroid aspect". Also presented corpus callosum, internal capsule and cerebellar involvement; 4/49 Krabbe disease, 4/4 symmetrical and bilateral WM, corpus callosum, posterior limb of internal capsule, pyramidal tracts and cerebellar involvement. 32/150 Mitochondrial Diseases; 9/9 MELAS with stroke-like WM involvement, 1/8 Leigh showed diffuse WM involvement. 21/150 Peroxisomal Disorders; 4 neonatal Adrenoleukodystrophy and Zellweger showed hypomyelination; 16/17 X-linked Adrenoleukodystrophy with parieto-occipital WM and splenium involvement, 1/17 showed anterior pattern. 2 Molybdenum Cofactor Deficiency showed multicystic encephalomalacia.

Conclusion. In our patients, more than half showed WM involvement, with characteristics for each disease, which reflects the susceptibility of WM metabolic changes, independent of the affected pathway.

FP130

MITOCHONDRIAL DNA DISEASE: CLINICAL SPECTRUM FROM THE GENOTYPE TO THE PHENOTYPE

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Introduction: Mitochondrial diseases are a group of maternally inherited disorders, clinically heterogeneous produced by mitocondrial DNA mutations. Clinical features related to a specific mutation are usually variable and multisystemic

Aim: To evaluate clinical manifestations, genogram, testing and evolution of patients diagnosed in our center with mitochondrial diseases and their phenotypic characteristics in relation to the genotype with different point mutations of mitochondrial DNA (A3243G, G11778A, A8344G).

Methods: Retrospective descriptive and monitoring of all patients with mitochondrialDNA mutations confirmed. Review of clinical records.

Results: 45 patients were studied 9 present with A3243G mutation 33 G11778A mutation and 3 A8344G mutation. In patients with A3243G mutation, average age of onset symptoms was nine years: headache (5/9), stunting (9/9), sensorineural deafness (8/9), cardiac disorders (2/9). They present stroke-like episodes (9/9) between 6 to 21 years, generalized tonic-clonic seizures (9/9). Study: elevated lactic acid plasma-CSF relation (9/9), ragged-red fibers (RRF)(7/9), CT/MRI: basal ganglia calcification (8/9), areas of infarction (stroke like) temporoccipital (9/9). Evolution: progressive, 3 died. Their relatives were affected by deafness, diabetes, and heart disease. 33 patients with G11778A mutation, 12 symptomatic. Presentation mean age 16 years, visual impairment (9/12), optic atrophy (7/12), impaired gait (4/12), dystonia (3/12). CT/MRI: putamens necrosis (4/12). Evolution: stable (5/12), slowly progressive (7/12). 3 brothers with A8344G mutation, average age presentation 10.6 years: all with myoclonic epilepsy, neuropathy, ataxia and FRR (+). Evolution: progressive.

Conclusions: In our series, A3243G mutation was related to mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) phenotype, G11778A mutation with Leber's optic neuropathy (LHON) phenotype and mutation A8344G with myoclonus epilepsy with ragged red fibers (MERRF) phenotype. Clinical manifestations, tests and maternally inherited form were the classically described for these phenotypes.

FP131

GLUTARIC ACIDURIA TYPE I (GA1), CLINICAL CARACTERIZATION AND GENETIC STUDY OF 11 CHILEAN CHILDREN.

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Introduction: GA1 is a metabolic disorder produced by a defect on glutaryl CoA dehydrogenase (GCDH) enzyme, in the GCDH gene localized in 19p13.2 chromosome.

Aim: To analyze clinical manifestations, neurologic evolution, imagenologic characteristics and type of mutations found in children with diagnosis controlled in our service.

Materials and Method: Retrospective-descriptive study and prospective analysis of 11 children diagnosed in our center in the last 17 years, with positive genetic study.

Results: Of a total of 11 patients, six were male. Eight debuted with an encephalitis-like episode at a mean age of 9,9 months. The three remaining patients debuted with psychomotor delay (mean age 4 months) with two of them presenting an encephalitis-like crisis later. Three patients progressed with macrocephaly. One patient

presented mild, two moderate and eight severe disability. Cerebral RM in acute episode showed basal ganglia and white matter compromise, bifrontotemporal atrophy, progressing to striatal atrophy. Residual enzymatic activity was deficient in four patients who were studied. Mutations found were heterozygous to R161Q/R402W, Y133H/R161Q, Y133H/R402W, V133/A385V and homozygous to R402W/R402W, A293T/A293T, Y113H/Y113H. No relationship was found between neurologic severity and specific genotype.

Conclusion: In our series, the most frequent presentation was an encephalitis-like episode. The most invalidating symptoms were extrapyramidal and neuroimages were distinctive. The homozygous and heterozygous mutation in Y113H and R402W are frequent in Chilean population, being Y113H exclusive in this population. The biochemical genotype and phenotype did not predict clinical course. In conclusion, presymptomatic diagnosis of this affection allows an appropriate management with a favourable evolution.

FP132

CONGENITAL METABOLISM DISEASES OF NEUROTRANSMITTERS IN PEDIATRIC NEUROLOGY: CLINICAL DESCRIPTION AND NEUROLOGICAL TRACING OF A GROUP OF PATIENTS.

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Introduction: The neurological manifestations of congenital metabolism diseases of aminergic neurotransmitters (NT) are diverse. The autosomal dominant Dopa-responsive dystonia (DRD), with deficiency of GTP cyclohydrolase1 (GTPCH1), is the most common type, with a satisfactory response to treatment. We describe clinical features, response to treatment and outcome of patients diagnosed with inborn errors of aminergic neurotransmitters in our center.

Methods: A retrospective descriptive study and a prospective follow-up of 17 patients. Review of clinical records.

Results: 17 patients. 16/17 exhibit DRD. 12/16 women. On 9/16 the average was 5 years age at onset and 9.5 years at diagnosis. In all patients the initial symptom was gait disturbance with diurnal fluctuation, lower limb (8/9) and upper limb (8/9) dystonia, trunk dystonia (3/9), tremor (3/9). Adult relatives (7/16) begin symptoms between 20 and 40 years: focal dystonia, parkinsonism. The mode of inheritance was autosomal dominant. The phenylalanine test was guiding. Diagnosis is confirmed with measurement of CSF levels of NT: low concentrations of neopterins, biopterins and 5HIAA HVA suggest deficiency of GTPCH1. Positive genetic study in 2 families. The response to levodopa treatment was satisfactory. One patient (1/17) shows a deficit of L-Dopa decarboxylase with severe global psychomotor retardation, fever, hypotonia, epilepsy, dystonia, and fatal outcome.

Conclusions: In our series predominates DRD, with clinical features and response to treatment classically described. Early diagnosis allows prompt treatment with improvement of symptoms and favourable course.

FP133

CLINICAL PROFILE OF CHILDREN WITH BIOTINIDASE DEFICIENCY AND RESPONSE TO ORAL BIOTIN THERAPY: EXPERIENCE FROM A DEVELOPING COUNTRY

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Aim: To study the clinical profile of children with biotinidase deficiency and their response to oral biotin.

Methods: Twenty-six consecutive patients with biotinidase deficiency diagnosed from September 2004-November 2013 were retrospectively reviewed. Initiation of biotin treatment was considered early (<6 months) and late (>6 months of age); responses were compared.

Results: Mean age at symptom-onset was 7.7 months (10 days-48 months). Developmental delay (65%), neuroregression (58%), seizures (81%), skin changes (65%), scanty hair (69%) and characteristic rash (31%) were noted at presentation. Generalized tonic-clonic seizures were (61.5%) preponderant. Microcephaly was seen in 35% and hypotonia in 65%. One child had macrocephaly. Perinatal-period was normal in 80%; one child had parental consanguinity. Common electroencephalography abnormalities were generalized spikes/spike-wave-complexes (31%), burst-suppression (15%), focal slowing (11%) and hypsarrhythmia (3%). Common magnetic-resonance-imaging abnormalities were diffuse cortical atrophy (31%), delayed myelination (8%) and non-specific white-matter hyperintensities (8%). Mean serum biotinidase level was 2.28 nmol/min/ml (range 0.08-5 nmol/min/ml). Oral biotin 10-20 mg/day was initiated in all patients; 50% were in early-treatment group. Mean follow-up period was 33.5 months. One patient was vegetative at 9 years of age and two patients died; 77% patients symptomatic relief following biotin therapy. Neurological sequelae noted were intellectual impairment, developmental delay, seizures, hyperactivity and vision-hearing impairments. Poorer seizure control (70% vs 85%), developmental delay (62% vs 70%) and hyperactivity (77% vs 92%) were noted in late vs early-treatment groups respectively.

Conclusion: Early recognition and prompt initiation of life-long biotin therapy helps in early seizure control and improved neurological outcomes.

FP134

ABNORMAL PUPILLARY LIGHT REFLEX WITH CHROMATIC PUPILLOMETRY IN GAUCHER DISEASE; RELATION TO PHENOTYPE AND THERAPEUTIC RESPONSE WITH CHAPERONE THERAPY

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Aim: The hallmark of neuronopathic Gaucher disease (nGD) is oculomotor abnormalities. The saccadic initiation failure (SIF) is well known, whereas assessment of SIF is difficult when examining uncooperative patients. While chromatic pupillometry is known as an objective method for evaluate the pupillary lightreflex (PLR), it has not been studied yet. In this study, we assessed the PRL with chromatic pupillometry to evaluate its utility for detection of neurological feature and therapeutic response of chaperone therapy in nGD.

Methods: Ten GD patients (1 GD1,5 GD2, and 4 GD3 patients) and 35 healthy controls were enrolled. All GD patients underwent enzyme replacement therapy (ERT) prior to PRL examination. After PRL examination, 5 patients (2 GD2 and 3 GD3 patients) received chaperone therapy (ambroxol: ABX) combined with ERT. A binocular infrared pupillometer, Iriscoder Dual C10641 (Hamamatsu Photonics, Hamamatsu, Japan) was used, and blue and red stimuli of 100 cd/m2 were selected in this study.

Results: In nGD, red light-induced PLR was markedly impaired, whereas blue light-induced PLR was relatively spared. In contrast, GD1 patient had no abnormalities. Combined ERT and ABX therapy has resulted in a marked improvementof red light-induced PLR for all treated patients.

Conclusion: NGD patients have PLR impairments, and chromatic pupillometry appears to be a useful method for evaluating such patients, regardless of age or neurocognitive status. Further studies are required to investigate the possibility of using PRL as a new marker for early detection and for monitoring the course of disease and response to treatment.

FP135

2-HYDROXYGLUTARIC ACIDURIA IN SAUDI ARABIA

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Background: 2-HydroxyGlutaric Acid (2HGA) is a dicarboxylic acid synthesized from 2-ketoglutarate and 4-hydroxybutyrate via malate dehydrogenase and ALDHFE1 respectively. Urinary excretion of small quantities of 2HGA is normal in healthy individuals. Known disorders of 2HGA metabolism associated with significantly elevated urinary excretion include: D, L and combined 2 hydroxyglutaric aciduria. Clinical phenotypes of these neurometabolic syndromes include neonatal/early-infantile onset encephalopathy, severe developmental delays, hypotonia, seizures, muscle weakness, cardiomyopathy, apnoea and multifocal cerebral white matter abnormalities. Current investigational therapies include AG-221 (Agios) for type II D-2 hydroxyglutaric aciduria and Taurine in SSADH deficiency.

Aim: To report on a large cohort of patients with 2-hydroxyglutaric aciduria diagnosed at KFSHRC.

Methods: Random urine samples from Saudi children with static as well as progressive neurodevelopmental disorders were evaluated by GC-MS analysis followed by LC-MSMS chiral analysis of the D and L enantiomers of 2-hydroxyglutaric acid.

Results: Since 1995 and among 3197 samples which were abnormal for various inborn errors of metabolism, 27 patients (8.4/1000) with significant 2-hydroxyglutaric aciduria were identified. Chiral analysis confirmed L-2HGA (15 patients), D-2HGA (3 patients) and combined D, L-2HGA (5 patients). One patient had D2-HGA in combination with 4-hydroxybytric aciduria.

Conclusion: L-2HGA is more common among Saudi patients with 2HGA. D-2HGA in combination with 4-hydroxybutyric aciduria likely results from altered activity of ALDHFE1 in combination with recessive germline mutations in SSADH. Accurate diagnosis of the specific etiology of 2HGA is essential for proper management, prognosis, genetic counselling and more recently, potential enrolment in prospective clinical trials.

FP136

MITOCHONDRIAL MOLECULAR GENETIC MUTATIONS FOUND IN A SOUTH AFRICAN POPULATION 1992-2012

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There is little known or published about the prevalence of primary mitochondrial respiratory chain disease in Africa, owing to resource restraints and the necessary prioritisation of health funding for preventable disease.

Aim: To review the pattern of common mitochondrial genetic mutations identified in a genetically diverse South African population from 1992-2012

Method: PCR analysis and standard methods of restriction enzyme digestion and/or sequencing of mitochondrial and autosomal DNA from blood, fibroblasts, urine and or muscle were performed as part of clinical diagnostic service.

Results: There were 907 referrals for analysis. 211 (23%) samples were from persons of indigenous African ancestry; the remainder were of European or mixed descent. Sixty three patients had mutations (7%). The most common was mt.3243A>G, MELAS (n=17). Mt.8993T>C NARP occurred in 9 patients, 8 from the same mixed ancestry family. Unusual mutations included Leigh Syndrome (LS) with mt.13094T>C, LS with mt.14597T>C, and two unrelated children found to be compound heterozygous for a known splice site mutation (c.751+6T>G) and an undescribed p.56 Ala>Gly in exon3 of the Surf1 gene. 5/10(50%) of patients with common deletions and 5/53 (9%) patients with point mutations had indigenous African ancestry. The incidence of positive test results was 4.7% (10/211) in the African sub population compared with 7.5% (53/706) in the rest of the group.

Conclusion: There is a trend for presentation with common deletions to be more prevalent than common point mutations in this Sub Saharan indigenous African population. Further research is indicated to validate these observations.