METABOLIC DISORDERS

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NOVEL PEX3 MUTATIONS IDENTIFIED AS THE CAUSE OF A PEROXISOMAL BIOGENESIS DISORDER WITH MODERATE CLINICAL PHENOTYPE

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Background: Peroxisome biogenesis disorders (PBDs) may have variable clinical expression, from severe, lethal to mild phenotypes with progressive evolution. PBDs are caused by mutations in PEX genes, which encode proteins, called peroxins, involved in the assembly of the peroxisome.

Objectives: To report a patient heterozygous for two novel mutations in the PEX3 gene with less severe phenotypic expression than reported previously for PEX3 patients.

Case Report: A five years old boy, first child of unrelated parents, presented with psychomotor retardation, axial and peripheral muscular hypotonia and nephrocalcinosis at 3 months of life. He was born at term, and perinatal history was uneventful. At 18 months old he presented progressive spastic paraparesis, neurogenic bladder and nystagmus that evolved to bilateral cataract at 4 years old.

Methods: Peroxisomal parameters were studied in cultured skin fibroblasts. PEX genes were sequenced in DNA isolated from fibroblasts.

Results: Catalase immunofluorescence showed a peroxisomal mosaic pattern with all cells containing peroxisomal membrane structures. Immunoblotanalysis for acyl CoA oxidase and peroxisomal thiolase was normal. Sequencing identified two heterozygous, pathogenic mutations in the PEX3 gene.

Conclusion: Our patient expands the clinical spectrum for PEX3 patients, because PEX3 mutations usually result in a severe, early lethal phenotype

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MANAGEMENT OF PATIENTS WITH ADRENOLEUKODYSTROPHY

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Introduction: X-linked adrenoleukodystrophy (X-ALD) is the most-common peroxisomal inborn error of metabolism. Currently, the only effective treatment in the cerebral phenotype is allogeneic hematopietic stem-cell transplantation (HSCT) in selected cases meeting the outcome criteria by Peters C. et al. The aim of this study was to present a working model for the assessment of X-ALD patients in a multidisciplinary team consisting of neurologists and specialists in inborn errors of metabolism, bone-marrow transplantation, imaging, endocrinology, cognition and mental health.

Material and methods: Of 25 patients seen, 16 were symptomatic and nine asymptomatic with elevated plasma very long chain fatty acids. Neurofunctional (Raymond scale),neuroradiological (Loes score), and cognitive (WISC IV) criteria were assessed. Criteria for HSCT were according to Peter C et al.

Results: Of the 15 symptomatic patients, 11 HSCT was not indicated because of advanced disease. All patients received symptomatic treatment (hormone-replacement therapy). Four were candidates for HSCT. Two received HSCT (one died 9 months after transplantation) and two possible donors are looked for. Of the presymptomatic patients (10), five received preventive dietary treatment (Lorenzo's oil and diet). One patient with endocrinological manifestations (pure Addison's) is also under control.

Conclusion: We consider that X-ADL patients should be evaluated by a multidisciplinary team from disease onset to provide adequate management and follow-up of the disease and its comorbidities as well as family counseling. Lamentablemente la mayoría de los casos índices no cumplen criterios para HSCT

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BIOPTERIN DISORDER CAUSING HIPERPHENYLALANINEMIA: TWO DIFFERENT CASES

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Hyperphenylalaninemia (HPA) may rarely be caused by defects in the synthesis or recycling of tetrahydrobiopterin (BH4), an essential co-factor in the phenylalanine hydroxylase activity (PAH) reaction. Approximately 2% of patients with HPA have a defect in one of the four enzymes responsible for maintaining BH4 levels. Guanosine triphosphate cyclohydrolase (GTPCH) and pyruvoyltetrahydrobiopterin synthase (PTPS) are essential enzymes for biosynthesis, whereas pterin-4α-carbinolamine dehydratase (PCD) and dihydropteridine reductase (DHPR) are responsible for recycling. The case report is about two different children with two years old, one of them with defect in GTPCH and other in DHPR. P.S.F. presented hypotonia with 3 months and constated a delayed neuropsychomotor developmental (DNMD) in the first year of life. Neurologic exam certified pyramidal signs and trunk hypotonia. During the diagnostic investigation, was observed HPA with abnormal values, but no high, which seems not compatible with phenilketonuria (PKU) diagnostic. The possibility was a secondary HPA, with a different enzyme defect. Complementary exam estabilished very low levels of neopterin and biopterin that indicates GTPCH defect. Other child, J.P.F.S., began clinical manifestations with epilepsy around 2 months and DNMD. The parents are consanguines. Neurologic exam demonstrated irritability and hypotonia. The inborn metabolism errors screen showed elevated seric phenylalanine and normal tyrosine. Adicional laboratory investigation confirmed DHPR absent activity. Biopterin disorders result in deficiencies of the neurotransmitters L-dopa and 5-hydroxytryptophan. Should be highlighted the early treatment could be modify the prognostic and register a rare cases of HPA without PKU.

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TAY-SACHS DISEASE B1 VARIANT: CASE REPORT

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Tay-sachs disease (TSD) is a lysosomal storage disorder which has autosomal recessive inheritance and low incidence. Occurs due to hexosaminidase A (HEX-A) enzyme deficiency in α subunit. The B1 variant is resulted from an altered substrate specificity of HEX-A, wherein the mutated enzyme retains the ability to degrade the artificial substrate but not the sulfated or natural substrate in vivo. The highest incidence, 3, 1 per 100.000 live births, for B1 variant of GM2 gangliosidoses has been described in Portugal, which has been suggested as the point of origin of a founder mutation seen in Brazilian patients. The case report is about a three year old male child, who presented one year earlier with regression on gait, speech and coordination. Then, he develops swallow disturbance and spasticity. The child was admitted to clinical investigation and diagnostic procedures. MRI and cerebral spinal fluid were normal. The inborn metabolism errors screen for HEX-A activity was normal, but when this exam was performed in another substrate (sulfatide) it was deficient, that is called HEXA MUGS activity. This variant B1 diagnose of TSD is rare variant disease and can be performed with this test. The genetic counselling was explained to parents giving the information about 25% of chance to descendent recurrence. The importance of this case is the challenge to make a differential diagnosis of acute ataxia in childhood and pay attention to progressive symptoms presence, which other pathologies must be suspected, like metabolic diseases.

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"MUCOPOLYSACCHARIDOSIS TYPE IV A: EVIDENCE OF PRIMARY AND SECONDARY CENTRAL NERVOUS SYSTEM INVOLVEMENT"

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Introduction: Mucopolysaccharidosis type IVA is a rare lysosomal storage disease caused by a deficiency of N-acetylgalactosamine-6-sulfatase. Studies usually focus on skeletal abnormalities and their consequences. This study explores the neurological manifestations in a cohort of mucopolysaccharidosis type IVA patients, with a detailed focus on brain and spinal MRI findings.

Methods: We performed a cross-sectional study involving nine patients with a biochemical confirmation of mucopolysaccharidosis type IVA. The protocol consists of a comprehensive clinical examination and brain/spinal cord MRI analysis for all subjects.

Results: The mean age was 16.4 years (± 5.7) and the mean onset of symptoms was 11.5 months (± 6.3). Overall, cognition was spared in all but one patient, motor weakness was a constant finding in all patients, and deep sensation impairment was found in six patients. The brain MRIs showed non-specific white matter changes in two patients; other abnormalities such as clival hypoplasia, basilar invagination, and arachnoid cists were seen in seven of the nine patients. Eight patients presented spinal cord compression, and in three of them, two spinal levels were compromised. Odontoid hypoplasia and degenerative features in the neuroaxis were present in all patients.

Conclusion: Our experience with mucopolysaccharidosis type IVA patients supports the evidence of CNS involvement. We emphasize the importance of regular clinical assessments with complete MRI studies, as an attempt to detect the early signs of spinal cord compression. This evaluation may be especially important before surgical interventions, as occult lesions may become symptomatic and promote postoperative unfavourable outcomes.

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"REMOTE SPINAL CORD INJURY IN MUCOPOLYSACCHARIDOSIS TYPE IVA AFTER CERVICAL DECOMPRESSION"

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Introduction: Mucopolysaccharidosis type IVA (MPS IVA, Morquio A syndrome, MIM #253000) is an autosomal recessive lysosomal storage disorder, characterized by inability to break down keratin-sulfate and chondroitin-6-sulfatase. Skeletal changes may result in disabling neurological complications. Atlantoaxial instability and cervical spinal cord compression are common; posterior occipitocervical fusion with (or without) spinal decompression is recommended.

Method: Case description. This report describes a patient who required occipitocervical fusion and suffered an irreversible thoracic paraplegia in the immediate postoperative period.

Case description: A 17 year-old boy diagnosed with MPS IVA at the age of 5, had slowly developed progressive signs of spinal cord compression. Prior to surgery, his neurological examination showed MRC grade 3 in the upper limbs and 2 in the lower limbs, hyperactive deep tendon reflexes without clonus or Babinski sign, and no sensorial impairment. His spinal MRI showed atlantoaxial subluxation and signs of myelomalacia at C1-C2 levels. Postoperatively, after occipitocervical fixation in the prone position, he developed acute paraplegia, sensory losses below T3 and striking MRI abnormalities far from the maximum compression site.

Discussion: MPS patients may develop remote spinal cord injuries from maximum compression sites after general anaesthesia in the prone position due to impaired cardiac output. The role of intraoperative monitoring with motor and/or somatosensory evoked potentials remains controversial in literature; although evoked potentials may indicate early signs of spinal infarct, they cannot prevent this unexpected complication. This outcome is unusual, but healthcare professionals, patients and their parents should be aware to this devastating complication after spinal cord decompression. ***Neurology*** April 15, 2014 vol.82 no. 15 1382-1383. Copyright © 2014, AAN Enterprises, Inc.

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"NEW INSIGHTS IN MUCOPOLYSACCHARIDOSIS TYPE VI: NEUROLOGICAL PERSPECTIVE"

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Objective: Mucopolysaccharidosis type VI is a rare autosomal recessive storage disorder, caused by a deficiency of arylsulfatase B. Data on neurological involvement in mucopolysaccharidosis type VI patients under enzyme-replacement therapy are limited. This study explores the neurological and magnetic resonance imaging findings in a sample of mucopolysaccharidosis type VI patients receiving enzyme-replacement therapy**.**

Methodos: We performed a cross-sectional study including six patients with biochemical confirmation of mucopolysaccharidosis type VI and at least two consecutive years receiving intravenous enzyme-replacement. The protocol included a comprehensive clinical examination, brain and spinal cord magnetic resonance imaging for all subjects.

Results: Overall, cognition was spared, while we found presence of hearing impairment, increasing in deep tendon reflexes, and deep sensation reduction in three patients. In addition to the classical mucopolysaccharidosis abnormalities, brain image studies demonstrated: (i) morphological changes in anatomy of middle cranial fossa; (ii) sella shape abnormalities; (iii) diploic thickness over venous sinus; (iv) dolicochephaly; (v) and sinus pericranii. Even in asymptomatic or mild compromised patients, spinal cord compression was found. In four patients we noticed atlantoaxial joint subluxation and three had cervical spinal stenosis. Degenerative processes involving vertebral column, including vertebral bodies' indentations, disc-osteophyte complexes, and Schmorl's nodes were present in all patients.

Conclusions: Neuroaxis involvement was a constant finding in our small sample; unfortunately, neurological examination might not predict the severity of the disease in course. Moreover, imaging studies should not be performed according exclusively clinical parameters, once we have demonstrated that neurological involvement may be silent in mucopolysaccharidosis type VI.

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CLINICAL AND RADIOLOGIC FEATURES IN 12 PATIENTS WITH JUVENILE AND ADULT GM1 GANGLIOSIDOSIS.

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Introduction: GM1 Gangliosidosis is an autosomal recessive disorder caused by B-galactosidase deficiency. It is a rare neurodegenerative disorder with three main clinical forms according to age of onset.

Methods: We performed a prospective study including full neurological examination and neuroimaging in 12 patients from 10 unrelated families.

Results: Consanguinity was denied in all cases but in two families there was recurrence in the sibship. Age at onset ranged from one to 12 years. All patients had short stature and dysostosis multiplex. Neurological involvement was present in all, especially extrapyramidal signs (10/12) including dystonia and chorea mainly affecting the facial segment. All patients presented with dysarthria often progressing to complete anarthria. Pyramidal signs were present in 8/12 patients; cognitive or behavioral abnormalities were reported in 5/12 patients, and mild oculomotor alterations were observed in all subjects who collaborated with the examination. Six patients were submitted to MRI evaluation. All presented with supratentorial volume loss, T2/FLAIR

hyposignal at globus pallidus, and FLAIR hypersignal at posterolateral putamina. Reduced putaminal volume and cervical vertebral alterations were also noted.

Conclusions: This large case series for such a rare disorder showed pyramidal and extrapyramidal signs in most patients, which were previously well known in this condition. In addition, we detected cognitive or behavioral impairment in half of the patients, and also mild oculomotor abnormalities not previously reported in this condition. MRI confirmed abnormalities in basal ganglia in all subjects submitted to this exam.

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DIFFERENTIAL DIAGNOSIS OF THE CHRONIC ENCEPHALOPATHIES: THE IMPORTANCE OF FOLLOWING THE PSYCHOMOTOR DEVELOPMENT MARKS

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Objectives: Emphasize the need to search, in different evolutive moments, the etiology of psychomotor development deviations to distinguish the chronic non-progressive encephalopathies from the progressive ones through the description of a late diagnosis of a Niemann-Pick type C disease (NPC) with a previous diagnosis of chronic non-progressive encephalopathy.

Case report: JPPP, male, 3 years old, first presented with motor development delay, followed by a delay in language acquisition. A MRI in 2011 suggested CMV lesion and two USG in the same year appeared normal. Follow up showed progressive motor losses and worsening of cognition. New investigation in 2012, revealed vertical supranuclear gaze palsy, ataxia, eventual dysphagia and splenomegaly. Bone marrow aspiration showed ***crinkled-paper***cytoplasm cells, questioning Gaucher disease. As the enzymatic test was negative and the patient evolved with gelastic cataplexy, it was initiated the research to NPC with a Niemman-Pick suspicion index (NP-SI) of 142 points. The hypothesis was confirmed by a positive Filipin test. In June/2013 Miglustat was initiated as substrate reduction therapy, and imipramine to cataplexy.

Conclusion: NPC is rare and polimorphic making it difficult to diagnose, specially when the visceral signs present themselves later. The use of the Niemman-Pick suspicion index oriented the investigation and helped in the case elucidation. This case makes clear that systematization is essential for the differential diagnosis of the psychomotor development delays.

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TETRAHYDROBIOPTERIN (BH4) DEFICIENCY: A CASE REPORT

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Introduction: Tetrahidrobiopterin (BH4) is an essential cofactor for phenylalanine, tyrosine and tryptophan hydroxylase and its deficiency results in hyperphenylalaninaemia and depression of neurotransmitters in the central nervous system. It is caused by defects in one of four enzymes responsible for its synthesis or regeneration. Typically manifests in the neonatal period or after the first year of life with motor delayed and / or cognitive impairment, hypotonia, movement disorders, seizures or autonomic symptoms.

Objective: To describe a case of tetrahidrobiopterin deficiency following in the Clinic of Metabolic Diseases, Hospital das Clinicas USP.

Case Description: Male, 3 years old, son of non-consanguineous parents, with no relevant gestational history, when he was asymptomatic with 7 days of life received neonatal screening for phenylketonuria changed. Initiated dietary restriction without a satisfactory answer. Evolved with hypotonia, developmental delay, gait ataxia and choreiform movements in hands. Introduced sapropterin with symptom improvement, currently presenting language delay. Biopterin and neopterin undetectable in urine and normal dihidropterin reductase activity. Tomography and magnetic resonance of brain unchanged.

Discussion / conclusion: The tetrahydrobiopterin metabolism disorders are rare forms of hyperphenylalaninaemia, representing 2% and make differential diagnosis with phenylketonuria, but more severe, worse therapeutic response and substantially different treatment. The suspected diagnosis by neonatal screening with subsequent early confirmation by specific laboratory tests are extremely important because they allow proper treatment and prevention of progressive neurological damage.

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INSIGHTS INTO THERAPEUTIC MECHANISM OF L-ARGININE THERAPY ON CEREBROVASCULAR REACTIVITY AND CEREBRAL BLOOD FLOW IN MELAS SYNDROME

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Background: MELAS syndrome is characterized by recurrent stroke-like episodes that constitute a major source of morbidity and mortality. The latter are presumed to result from both direct neuronal energy failure and functional angiopathy. It has been suggested that L-arginine reduces frequency and severity of stroke-like episodes, but the underlying mechanism is unclear.

Methods: We performed a case control study in 3 siblings with MELAS syndrome to evaluate baseline cerebrovascular reactivity (CVR) and perfusion using BOLD-fMRI. We then conducted a prospective clinical trial pilot study to assess the response of these parameters to single dose and 6-week steady-state oral L-arginine.

Results: MELAS subjects had lower serum arginine levels, and demonstrated decreased CVR and increased cerebral perfusion at baseline relative to controls. The latter abnormalities correlated with percentage of mutant mtDNA in blood. On regional analysis, mean CVR was reduced to a greater degree in frontal compared to occipital cortex. Following L-arginine therapy, MELAS subjects showed an increase in CVR in frontal cortex and a corresponding decrease in occipital cortex; CVR globally was unchanged. There was a dramatic reduction in hyperperfusion following steady state L-arginine in one MELAS subject.

Discussion: Interictal vascular reactivity and cerebral perfusion are abnormal in MELAS syndrome in accordance with disease severity. L-arginine therapy does not improve overall CVR interictally; however, it seems to selectively improve CVR in the regions that are most impaired at the expense of less abnormal regions. It may also decrease hyperperfusion, possibly by improving energy metabolism or normalizing vascular tone.

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RAPID CLINICAL AND NEURORADIOLOGICAL REVERSAL OF STROKE-LIKE EPISODES IN MELAS SYNDROME FOLLOWING HIGH DOSE L-ARGININE

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Introduction: Pathophysiology of stroke-like episodes (SLEs) in MELAS (**M**itochondrial **E**ncephalomyopathy, **L**actic **A**cidosis and **S**troke-like episodes) is presumed to involve mitochondrial energy failure causing neuronal injury and microangiopathy. L-arginine (L-Arg) during acute SLEs may be associated with a reduction in severity of SLEs.

Case description: A 10-year-old boy with mtDNA A3243G tRNA Leu mutation presented with acute encephalopathy, right focal seizures, motor apraxia and expressive aphasia. MRI showed left temporal lobe gyriform cortical diffusion restriction with mass effect. He was treated with oral L-Arg 500 mg/kg/d and within 24 hours showed rapid improvement of symptoms. He suffered repeated emesis of his L-Arg with recrudescent encephalopathy, apraxia and aphasia. He was started on iv L-Arg 500mg/kg/d for 24 hours and then 200mg/kg/d for 48 hours and symptoms quickly reversed again to baseline. L-Arg was then slowly tapered to 1 g tid po maintenance. At 13 years, he presented with an URTI and emesis. Six days later he suffered acute intermittent frontal headaches with transient diplopia and vomiting. MRI showed new symmetric lesions of the putamen and lesion of the right pons. He was again treated with high dose iv L-Arg. Within 24 hours he had complete resolution of symptoms. MRI repeated 3 days later showed resolution of the pontine lesion.

Discussion: L-Arg is converted to nitric oxide, which is important in vasodilation and is a precursor for creatine and may improve TCA cycle anaplerosis. The consistent reversal of SLEs following high dose L-Arg in this case supports a therapeutic response.

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QUANTITATIVE MEASUREMENT OF CEREBRAL OXYGEN EXTRACTION FRACTION USING MRI IN PATIENTS WITH MELAS IN DIFFERENT PHASES

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Aim: We aimed to quantify the cerebral OEF using MR in patients with MELAS in different phases.

METHOD AND MATERIALS: From December 2009 to December 2013, 42 patients with MELAS were examined by MR, nineteen patients in the acute and subacute phase (group 1), and 23 patients in the interictal phase (group 2) were included. Twenty-six healthy volunteers (group 3) were recruited for control subjects.

A newly-designed sequence, named gradient-echo sampling of spin echo (GESSE), was applied to obtain the cerebral OEF data on the axial section just above the lateral cerebral ventricle. Six regions of interest (ROI) were placed on the section. We obtained six OEF values and then calculated the mean value, which was the cerebral OEF of this section. In the 17 patients with unilateral cerebral involvement in acute and subacute phase, additional ROIs were placed on the lesions and the uninvolved contralateral counterparts.

RESULTS: Significant difference in cerebral OEF was found among different groups. OEF was reduced in the patients with MELAS compared with normal people, and the OEF values in the acute and subacute lesions were lower than those in the interictal phase. (acute and subacute phase: 0.271±0.007; the interictal phase: 0.293±0.002; volunteers: 0.319±0.006, X^2 = 25.4, P<0.001). Fifteen of 17 selected ROIs have lower values than the uninvolved contralateral hemispheres (Z =-2.20, P = 0.028).

CONCLUSION: Our study showed decreased utilization of oxygen in the brains of MELAS patients during different phases of this disease. The quantification of cerebral OEF, might be applied to evaluate the pathogenesis and prognosis of MELAS.

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CLINICAL, BIOCHEMICAL AND GENETIC SPECTRUM OF MITOCHONDRIAL DISORDERS IN EGYPTIAN CHILDREN: A STUDY OF 15 CASES

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Introduction: Mitochondrial encephalomyopathies are a growing group of diseases with a large variety of clinical presentations ranging from a well defined clinical syndromes to non specific manifestations as failure to thrive, hypotonia, seizures, global developmental delay, cardiomyopathy, visual or hearing loss. The objective of this study is to describe the clinical, biochemical and genetic spectrum of 15 Egyptian patients with confirmed mitochondrial respiratory chain disorder.

Subjects and Methods: This is a retrospective study which included 62 patients with and age ranging from 9 months-25 years referred to the neurometabolic Unit at Cairo University children Hospital for evaluation for a possible mitochondrial respiratory chain disorder. They were 35 males/27 females. All patients were subjected to thorough neurological examination, basic lab investigations, expanded metabolic screen and urine organic acid profile, muscle biopsy subjected toimmunohistopathological stain by COX and SDH, and respiratory chain complexes were assayed spectrophotometrically using specific substrates, and molecular diagnosis for mitochondrial syndrome.

Results: 15/62 patients has been confirmed with respiratory chain disorders. Three patients were diagnosed as MNGIE, one patient with MELAS, one patient with mitochondrial depletion syndrome, one patient with mitochondrial myopathy, 5 patients with complex I deficiency(1/5 presenting as biotin responsive striatal necrosis), 2 patients with combined complex 1 & IV deficiency, 2 patients with LHON.

Conclusion: Mitochondrial disorders have a wide spectrum of clinical presentations accounting for the marked delay in the diagnosis. High degree of suspicion is necessary to start a comprehensive work up combining clinical, biochemical, pathological and molecular data to confirm the diagnosis

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ROLE OF PLASMA AMINOACIDS AND URINARY ORGANIC ACIDS IN DIAGNOSIS OF MITOCHONDRIAL DISEASES IN CHILDREN

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Diagnostic difficulty in mitochondrial diseases (MD) results not only from the wide spectrum of symptoms and signs but also from the absence of a reliable screening or diagnostic biomarker.

Aim: To investigate the likelihood of MD in patients with symptoms and signs impressive of MD through quantitative measurement of plasma amino acids, and urinary organic.

Methods: Twenty patients with symptoms and signs suggestive of MD, were further evaluated by quantitative plasma aminoacids and urinary organic acids assay and neuroimaging.

Results: Plasma amino acid results revealed elevation of alanine in 11 patients, of Glycine in five and proline in two patients. Abnormal urinary organic acid analysis was present in six patients; increased urinary lactate (20%), dicarboxylicaciduria (15%) and urinary ketone bodies (10%). According to MD scoring system

(Wolf and Smeitink, 2002); upon enrollment our patients scored as possible MD. At end of study, five patients still scored as possible MD, eight patients were considered probable MD and seven patients as definite MD. All patients with definite MD had elevated serum lactate. Elevated urinary lactate in three patients was the only urinary organic acids abnormality in them. Plasma amino acid showed elevated alanine in all patients with definite MD, whereas proline was elevated in one. MRI brain showed atrophic changes in one patient and bilateral basal ganglia hyperintensity in another.

Conclusion: Urinary organic acids and quantitative plasma amino acids essay is a useful part of the work up for MD, especially when the economic burden and absence of specialized centers limits the diagnostic ability.

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FIRST CASE OF GLUT1 DEFICIENCY SYNDROME IN A 2-YEAR-OLD ESTONIAN GIRL: A CASE PRESENTATION

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Introduction: Glucose transporter-1 (GLUT1) deficiency syndrome is caused by heterozygous mutations in the SLC2A1 gene, resulting in impaired glucose transport into the brain and hypoglycorrhachia. The clinical spectrum is wide, but it is classically characterized by treatment-resistant epilepsy, developmental delay and complex movement disorders.

Case Description: The patient was born at term from normal pregnancy and delivery. She was consulted repeatedly by child neurologist due to delayed psychomotor development, central hypotonia, ataxia and seizures. Seizures started at the age of 10 months and at 1y 4 months she had had 3 generalized tonic-clonic seizures and 3 eye-rolling episodes. All interictal electroencephalograms were normal and she was treated with levetiracetam. Magnetic resonance imaging, at 10 months and 1y 5 months, showed changes in white matter signal, indicating to delayed myelination. Full metabolic work-up was negative, except elevated plasma alanine, suggestive of possible mitochondrial disorder. At 1y 5 months muscle biopsy was performed and mitochondrial disorders were excluded. At the age of 2y 1months cerebrospinal fluid (CSF) analysis showed low CSF glucose (2.0 mmol/l; normal range 3.3-4.4 mmol/l) and decreased CSF-to-blood glucose ratio (0.358) in the absence of hypoglycemia. Sequence analysis of SLC2A1 revealed a heterozygous mutation (c.968_972del p.V323Afs*56) and GLUT1 deficiency syndrome was diagnosed at the age of 2y 1months.

Treatment with ketogenic diet was started immediately with favourable response.

Conclusion: This is the first case of GLUT1 deficiency syndrome in Estonia. Recognizing GLUT1 deficiency syndrome is important, since it is effectively treated by ketogenic diet.

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P255

CHONDRODYSPLASIA PUNCTATA OR CONRADI-HÜNNERMANN SYNDROME. THE FIRST GUATEMALAN CASE

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AIM: Conradi - Hünnermann syndrome (CHS) is clinical and genetically heterogenous disorder characterized by punctiform calcification of the bones (1).The clinical features describe includes skin defect linear or whorled atrophic and pigmentary lesions, coarse lustreless hair, alopecia, cataracts, and skeletal abnormalities. We present a patient with this clinical feature, like the first Guatemalan case reported of CHS.

PATIENT: We present a girl of 18 months of age, product of third pregnancy, no prenatal or delivery problems, mother denied intake warfarin or any drugs during pregnancy, also denied consanguinity. Came to consult for development delay and short stature. The first consult occur at the age of 11 months, we found skin lesions: erythematous skin lesions, alopecia, ichthyosis form, atrophoderma, and coarse lustreless hair, Skeletal defects: macrocephaly with frontal prominence rizomelic shortening of the limbs, scoliosis. Also we found hypotonic posture, without weakness, osteotendinous reflex was normal, god visual contact language delay. The MRI made at 11 months shows brain atrophy with frontal pachygyria. The X ray show punctiform calcifications and injuries punch of the long bones, in femoral, humerus, tibia, and iliac bones. Several infections in the first year of life.

DISCUSSION: CHS it's a paroxysmal disorder who interfere with the normal formation of cholesterol. We present a first Guatemalan case, a girl with many clinical features described before in CHS, but also with characteristic not described yet, like macrocephaly with brain atrophy, and frontal Pachygyria. We believe that it`s part an spectrum of Peroxisomal Disorders

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LYSINURIC PROTEINURIA- FIRST GENETICALLY PROVEN CASE FROM FROM INDIA

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Lysinuric protein intolerance (LPI) is a rare autosomal recessive disorder affecting the basolateral transporter for cationic amino acids in the kidney and intestine leading to deficiency of these amino acids in blood (1, 2). Low levels of arginine and ornithine limit the functioning of the urea cycle resulting in high levels of ammonia accumulation affecting the brain and other organs.

A three year old child born following a consanguineous relationship had presented to us with an eight month history of daily episodic irritability lasting for up to 12 hours. There was associated slow cognitive regression. The child was being treated for epilepsy with multiple anticonvulsants without benefit.

His EEG was normal and MRI had shown symmetrical periventricular T2 Hyperintensities. On clinical examination he was pale, ataxic and had hepatosplenomegaly. His plasma ammonia was significantly raised at 840 micromol/l (normal range <35) as were plasma ferritin with mild derangement of liver function. Clinically Lysinuric proteinuric intolerance was suspected.

Plasma amino acids showed low levels of lysine, arginine and ornithine while urine aminoacidogram showed elevated level of these aminoacids. Urine organic acids were analyzed by GC-MS which demonstrated elevated levels of orotic acid (around 460 fold).

The child showed dramatic improvement in his symptomatology after starting ammonia scavenging therapy (Sodium benzoate and Citrulline) and mild protein restriction in diet. Ammonia levels had normalised.

The clinical and biochemical investigations are consistent with the diagnosis of LPI and gene studies subsequently confirmed a homozygous c.158C>T mutation in exon 1 of the gene for LPI

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MANGANESE TRANSPORTER DEFECT IN A CHILD: A RARE CASE REPORT

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Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in ***SLC30A10*** gene, a Manganese transporter in humans has been recently described. Because of hepatic involvement and extrapyramidal neurological manifestations, many cases are misdiagnosed and treated as Wilson's disease. We here report a 14-year old girl with manganese transporter defect that resulted from a novel mutation in ***SLC30A10*** gene from Southern India. Our patient, 2nd child born to a 2nd degree consanguineously married couple developed sub-acute hepatitis at 3-years of age that spontaneously resolved with supportive care. Three months later she developed insidious onset gradually progressive extrapyramidal features like drooling and feeding difficulties with abnormal posturing of limbs (right more than left). At 12-years, she developed dyspnoea secondary to polycythemia and underwent bloodletting twice. There was no evidence of KF ring in the cornea. Her MRI brain showed T1 hyperintensities (T2 isointense) in the basal ganglia, brainstem and cerebellum which were suggestive of manganism. Her manganese levels were elevated (9.8 microgm/l; range: 0.3-1.8) and genetic analysis showed a novel homozygous truncating mutation in the ***SLC30A10*** gene there by confirming the diagnosis of Managenese transporter defect. She was treated with antidystonic drugs and iron supplementation along with physiotherapy. Because of unavailability of BAL and disodium calcium edetate, antichelation therapy could not be offered. There was no further worsening (for last 12-months). To conclude, suspect manganese transporter defect in a child with hepatic involvement, extrapyramidal presentation and polycythemia with signal changes in the T1 weighted images in basal ganglia.

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PROFILE OF IEM CASES (SMALL MOLECULE TYPE) IN A TERTIARY CARE REFERRAL CENTRE FROM INDIA

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Objectives: To study profile of IEM cases - age of onset, common presenting features, effectiveness of treatment and short term outcome in children.

Methods: study period- Jan 2009-May 2012. Symptomatic children (unexplained encephalopathy, movement disorder, hepatomegaly, hypoglycemia, acidosis, etc.) screened with Blood gases, serum ammonia, lactate, TMS, urine GC-MS & HPLC. Long term outcome of diagnosed cases obtained during follow up visits and out-patient records. Microsoft XL based tools used to study distributions and trends.

Results: Among 1,422 high risk children screened 130 were positive for IEM (9.14%). 28.6% had family history of abortions, unexplained sibling deaths & siblings with similar complaints. Seventy nine percent presented in first year of life. Organic acidemias (OA) were commonest 69 (53%), Fatty Acid Oxidation Disorders 32(25%) & Amino Acid Disorders 24(18%). Methylmalonic academia (18), Glutaric aciduria-1(15) & Propionic academia (11) were common OAs. MSUD (8) &Tyrosinemia-1(6) common amino acid metabolism disorders. MCAD (12) & CPT-1(6) common FAODs. Disorders of Amino Acid Metabolism earliest onset and highest mortality. Infections were common triggers. Encephalopathy, Developmental delay, metabolic acidosis, hypoglycemia, hepatomegaly, hypotonia and diarrhoea major presenting symptoms. Fifty lost for follow-up. 80 patients who received specific interventions, 27.5% improved and an equal percentage had mortality (Neonatal mortality being the highest at 71.5%). 45% who received intervention survived with morbidity speech delay, motor delay, gross developmental delay and generalized dystonia.

Conclusions: Organic aciduiras are the largest group, post symptomatic treatment was associated with poor long-term outcome.

Hence the need for New-born screening in general population for presymptomatic diagnoses.

P259

MUTATION SPECTRUM OF GLUTARYL-COA DEHYDROGENASE DEFICIENCY IN SOUTH INDIAN POPULATION WITH GLUTARIC ACIDURIA TYPE I

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Glutaric Aciduria (GA I) is a commonly reported organicaciduria in India and the spectrum of mutations in the GCDH gene were not reported in the Indian population. Mutation analysis was done in twelve patients with biochemically confirmed cases of GA I. Glutaryl-CoA dehydrogenase (GCDH) gene was sequenced in these families and identified seven novel mutations in twelve families. The mutations were mostly missense. Homozygous mutations were seen in 9 families, one heterozygous mutation and a benign SNP in two families. No phenotype genotype correlation could be made except in those families with a benign SNP and heterozygous mutation where the phenotype was milder and response to treatment was good. Genetic evaluation is useful in counselling families with regard to prenatal diagnosis and reproductive options. Mutation analysis is a useful tool in the absence of availability of enzyme assay for GA I in India.

P260

CHRONIC PERIPHERAL NEUROPATHY PROGRESSING TO ENCEPHALOPATHY AS A RESULT OF LEAD INTOXICATION

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Here we report 2 cases of younger children who had persistent anorexia. In the course of time, with persistent exposure they developed peripheral neuropathy. One of the children remained undiagnosed for 4 months and with peripheral neuropathy .she progressed to the state of encephalopathy. In both cases the symptomatology was found to be due to lead intoxication.

Both of them were treated using chelation therapy. Use of D penicillamine was sufficient for treatment of peripheral neuropathy. For lead encephalopathy we had to use Inj. BAL and Inj.Edetate calcium in combination. Chelation therapy had given satisfactory improvement in both cases. Herbal medicine (Ayurvedic) given for the long period of time was the source of Lead. We recommend lead intoxication to be thought of in patients presenting with chronic neuropathy and a rare cause of encephalopathy .However any medicine whether it is herbal or not to be used judiciously.

P261

MULTIPLE CARBOXYLASE DEFICIENCY PRESENTING AS ACUTE ENCEPHALOPATHY

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We present a case of 6 months old female child who was born of nonconsanguineous marriage. She had normal neurodevelopment till the age of 6 months. On administration of top feeding with high protein formula, she developed respiratory distress followed by altered sensorium. She developed severe dystonia of both limbs. She had severe acidosis with moderately high lactate and ammonia. Her blood sugar was within normal range with normal range of all electrolytes. She was treated as metabolic acidosis with plenty of dextrose combined with insulin drip. MRI showed symmetrical lesions in globus pallidi which showed elevated choline and lactate peak on MR spectroscopy. There were punctate haemorrhages in right parietal rgion. Her tandem mass spectrometry showed very high C5 OH and urine gas chromatography revealed metabolites of multiple carboxylase deficiency. Her biotinidase enzyme assay was 3 microgram/dl. She was given biotin 10 mg twice a day. Initially, she was conscious with relief of dystonia she developed fulminating fungal infection of intestine later on. However she died of fulminating fungal septicemia. Multiple carboxylase is a rare autosomal recessive disorder which usually manifests in infancy. Good outcome with Biotin is well known but it could be fulminant in few. Our case reminds to institute compulsory new born screening for metabolic disorders in the developing countries like India.

P262

AN EXPERIENCE OF CHILDHOOD NEUROMETABOLIC DISEASES REGISTRY IN IRAN,2010-2012

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Introduction: Neurometabolic diseases are a diverse group of brain disorders. The main objective of our study was to collect clinical information of patients 0-19 years age with a clinical picture suspicious of neurometabolic disease in order to creation of a childhood neurometabolic registry system.

METHODS: During years 2010-2012 we collected clinical information's of patients with suspected neurometabolic disease according to two classification system: Dyken classification and the other system, small and large molecules disorders.

RESULTS: During two years, clinical data of 138 patients were collected. Based on Dyken classification, patients were divided as follow: 72 patients with classic and unclassified leukodystrophies, 28 patients with different types of poliodystrophies, 6 patients with diffuse encephalopathies and 3 patients with spinocerebellopathies. According to small and large molecules disorders patients were divided as follow: the first group (20 cases) and second group (34 cases).

DISCUSSION: we could obtain relative incidence of some neurometabolic disorders in Tehran province by isolating those patients that were residents in Tehran province. incidence of classic leukodystrophy and classic and unclassified leukodystrophy with together were 12.7 and 21.7 cases/1 million children. Relative incidence of inherited secondary leukoencephalopathies and total inherited white matter disorders were 5.4 cases/1 million children and 18.1 cases/1 million children, respectively. It seems that due to the high rate of consanguineous marriages in Iran, incidence and prevalence of neurometabolic disorders are very significant. Similar studies are also necessary to obtain a more accurate statics of neurometabolic disease incidence in Iran.

P263

A CASE OF LEIGH SYNDROME CAUSED BY 3-METHYLGLUTACONIC ACIDURIA

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Introduction: Leigh syndrome is a neurodegenerative disorder, characterized by symmetrical lesion of basal ganglia, thalamus, and brainstem. Dysfunction of the respiratory chain is the main cause of the disease, but no definite metabolic derangement is evident in 40-65%. We present a case of 3-methylglutaconicaciduria with clinical and neuroradiological findings of Leigh syndrome.

Case: A Four-year-old boy was born from non-related healthy parents. Nystagmus was noticed at 6 months. At 12 months, he showed developmental regression with hypotonia, nystagmus, and choreoathetosis. Brain MRI showed symmetrical hyper intensity of the basal ganglia and substantia nigra on T2WI, FLAIR, and DWI. Cerebrospinal fluid test showed increased level of lactate and pyruvate (25.4mg/dl and 2.21 mg/dl, respectively). Urinary organic acid profiles showed mild increase of 3-hydroxyisobutyrate. Respiratory chain complex was normal in muscle biopsy. Exon sequences of pyruvate dehydrogenase complex E1α showed no mutation. We diagnosed Leigh syndrome, and treated with vitamins, pyruvate and ketogenic nutrition. But triggered by febrile illness, psychomotor disability, hypotonia, dystonic movement, visual loss, deafness, and breath holding spells progressed. At age 2, urine metabolomic analysis and urine organic analysis showed mild elevation of 3-methylglutaconicacid. Fillipin staining performed in fibroblasts, showed mild accumulation of free cholesterol. We considered it to be 3-methylglutaconicaciduria with sensori-neural deafness, encephalopathy, and Leigh-like syndrome (MEGDEL syndrome). Now sequence analysis of SERAC1 is being performed.

Discussion: Leigh syndrome is caused by heterogeneous defects in energy metabolism. 3-metylglutaconic aciduria is a rare cause. Repeated urinary analysis and fillipin staining represent the diagnosis.

P264

X-LINKED ADRENOLEUKODYSTROPHY IN CHILDHOOD

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Purpose: X-linked adrenoleukodystrophy (ALD) is a rare disorder that shows a great deal of phenotypic variability. We subdivided childhood X- linked ALD patients into several phenotypes by the age at onset, the sites of most severe clinical involvement and the rate of progression of neurologic symptoms.

Methods: Fourteen patients who had been diagnosed as X- linked ALD and followed up for at least one year were enrolled from 1996 to 2010.

Results: 1. eleven had childhood cerebral ALD, who showed first neurologic symptoms at 7.29 years and progressed rapidly: interval between first symptoms and vegetative state was 1.48 years, and interval from initial symptoms to death was 3.44 years. Treatment with Lorenzo's oil did not prevent neurologic progression. Two patients who underwent umbilical cord blood transplantation died. 2. Two had adolescent cerebral ALD. They had first symptoms at 11.5 years, and showed tendency to progress less rapidly than childhood cerebral form patients. 3. One "Addison only" patient who had adrenal insufficiency without nervous system involvement remained asymptomatic during Lorenzo's oil treatment. 4. Most cerebral form patients except two showed the lesions in both parieto-ocipital white matter in brain magnetic resonance imaging.

Conclusion: The cerebral ALD was the most common form in childhood and was associated with a grave prognosis.

P265

BIOTIN RESPONSIVE BASAL GANGLIA DISEASE : UNUSUAL PRESENTATION WITH SPINAL CORD INVOLVEMENT

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Background: Biotin responsive basal ganglia disease (BBGD) is a recessively inherited disorder manifested as subacute encephalopathy .It is a rare disorder related to thiamine transporter II deficiency caused by mutation in ***SLC19A3*** gene. Administration of high dose of Biotin and thiamine resulted in significant improvement .Here we report 2 cases of BBGD with different clinical presentation and one with cervical spinal cord involvement.

Case (1): A 13- year- old girl who was previously healthy presented at the age of 11 years with seizure, confusion and abnormal gait. (CSF) analysis was normal. MRI brain showed multiple lesions of high signal intensity involving the basal ganglia, cerebral and cerebellar white matter with alteration in signal intensity of cervical spine. She was diagnosed initially as Acute Disseminating Encephalomyelitis (ADEM), received IVIG and methylprednisolone without much improvement. DNA test identifies mutation in ***SLC19A3*** gene. Administration of high dose Biotin and thiamine reverses the symptoms.

Case (2): A 2- year- old girl who presented with a 5 days history of unsteady gait, her brother died at age of 2 years with similar presentation. Her clinical examination showed dystonia. Laboratory investigations showed normal amino acids and urine organic acids profile. MRI brain demonstrated high signal intensity in subcortical white matter, red nuclei and basal ganglia bilaterally. DNA confirmed the diagnosis of BBGD. She responded dramatically to high dose of Biotin and thiamine.

Conclusion: BBGD is a rare disorder that should be suspected in patients with subacute encephalopathy and acute dystonia as early recognition and treatment prevents serious complications and eventually death.

P266

EPILEPSY AS A FORM OF PRESENTATION OF HYPERPROLINEMIA TYPE I: A PURPOSE OF TWO CASES

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OBJECTIVES: Hyperprolinemia type I (HPI) is an inborn error of metabolism caused by proline gene alteration proline dehydrogenase (PRODH) on chromosome 22q11, which causes increased levels of proline in plasma and urine by decreasing the activity of the proline oxidase (POX). Clinical manifestations can find cognitive and psychiatric disorders, epilepsy and kidney impairment. We present two cases with different clinical expression HPI.

CLINICAL OBSERVATIONS: The first case is a girl who presented development delay and hypotonia at birth and whose Exploration showed macrocephaly, prominent forehead, flattened nasal nose and hypertelorism. Family and personal history normal. With three years starts episodes of cessation of motor activity without automation or abnormal movements of seconds long. EEGs are displayed in several abnormalities multifocal. Shows increase in metabolic study of plasma proline and proline and hydroxyproline increased urine HPI diagnostic support.

The second case is a child with normal physical examination, personal history and family without interest starts at 2 years and 4 months simple partial seizures refractory to antiepileptic treatment. Several electroencephalograms show a right frontotemporal focus. On several occasions the patient had episodes of ataxia associated with fever and intake of certain drugs (phenytoin and oxcarbazepine). In which an increased metabolic study of plasma and urine proline, hydroxyproline and glycine increased in urine and increased glutamine cerebrospinal fluid compatible with all HPI.

COMMENTS: HPI can present with various clinical manifestations, among which predominate seizure. This entity should be included in the differential diagnosis of a child with epilepsy, especially if refractory.

P267

LIFE EXPECTANCY OF LEIGH SYNDROME IN INFANTS AND CHILDREN

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Introduction: Leigh syndrome, caused by dysfunction in mitochondrial energy metabolism, is an inherited, heterogeneous and progressive neurodegenerative disorder in infancy and childhood. The aim of this study is to analyze the life expectancy in patients with Leigh syndrome from clinical and genetic features.

Methods: From 1983 to March 2012, 30 patients diagnosed with Leigh syndrome by characteristic neuroimaging findings, abnormal histochemical stains and/or abnormal mitochondrial configurations of the muscle cells, and/or pathognomonic mitochondrial gene mutations.

Results: 22 of 30 cases presented clinical features before age of one year. All of them presented with variable symptoms of CNS involvement. The first three common symptoms were developmental delay, seizures, and altered level of consciousness. Extra-CNS manifestations were not uncommon, including pericardial effusion, cardiac rhythm disorder, ophthalmologic disorder, hearing impairment, liver function impairment, and failure to thrive. All of them showed abnormal neuroimaging findings over the basal ganglia and/or brainstem. 12 cases carried mitochondrial gene mutations, i.e., seven were T8993G, three were T10191C, one was A8344G, and one was A4316G. The prognosis for Leigh syndrome was poor during long-term follow up. 18 cases died of sudden apnea or respiratory failure before 1 year and 6 months of age. Three cases with T10191C mutation manifested longer life expectancy. The longest age was 17 years old.

Conclusions: Patients with mitochondrial T10191C mutation had a longer life expectancy as compared with that of other gene mutations in patients with Leigh syndrome.

P268

CHARACTERIZATION OF BEHAVIORAL AND SEIZURE RELATED MANIFESTATIONS OF GUANIDINOACETATE-METHYLTRANSFERASE DEFICIENCY.

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Guanidinoacetate methyltransferase (GAMT) deficiency is an autosomal recessive error of creatine synthesis characterized by cerebral creatine deficiency, accumulation of guanidinoacetate, mental retardation, epilepsy and extrapyramidal signs. Patients with GAMT deficiency have an unspecific but relatively constant clinical presentation.

We presented the behavioural and seizure related manifestations of two siblings with GAMT deficiency and compared their clinical phenotype to the related literature. Our patients, an 8-year and 14-year

old boys with GAMT deficiency, presented mental retardation, epilepsy and autistic behaviour. Diagnosis was done by brain magnetic resonance spectroscopy, biochemical and genetic procedures (guanidinoacetate quantification, determination of GAMT activity and mutation analysis in the GAMT gene). GAMT gene was analyzed by DNA sequence analysis: the homozygous c.326A>G mutation was detected. This mutation is predicted to result in a missense mutation (one amino acid replacement) or in erroneous splicing. The mutation was not detected before in any other patient with GAMT deficiency or in 13000 other controls.

GAMT deficiency is treatable; therefore, its early diagnosis might be critical, to prevent irreversible brain damage. It must be considered in the differential diagnosis of the broad range of unexplained neuropsychiatric disorders with epilepsy in children and it can be ruled out/detected by using brain magnetic resonance spectroscopy and/or by guanidinoacetate and creatine measurements in body fluids.

P269
INFANTILE NEURONAL CEROID LIPOFUCSINOSIS "CASE REPORT"

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Neuronal ceroid lipofuscinoses (NCLs; also known collectively as Batten Disease) are a family of autosomal recessive lysosomal storage disorders. Mutations in as many as 13 genes give rise to ~10 variants of NCL, all with overlapping clinical symptomatology including visual impairment, motor and cognitive dysfunction, seizures, and premature death.

Case Description: A four year- old boy, referred to our service with seizures and progressive neuromotor retardation. The patients and his family's history are not sprecific. The patients mental and motor development are normal until 18 months. After the 18th months the motor retardations begun with walking disorder. Follwing this, the patient had febrile and afebrile seizures. In physical examination the general condition moderate, the response to pain is just groaning. Bilateral light and corneal reflexses are absent. He is microcephalic (<3th percentile), The deep tendon reflexes in the lower extremities are more alert. He couldn't sit with support and also couldn't speak too. The laboratory tests including hemogram, serum biochemistry, metabolic screening were all normal. In cranial magnetic resonans imagination (MRI) there was cortical atrophy and volume deficit in the gyruses was shown. In electroencepahologram (EEG) in both temporo-occipital region, asencroniesd sharp wave forms were seen. After these finding further evaluation done and in genetic analyse; (1p32) c.559C>T (p.H187Y) homozygot mutation shown in the palmitoil protin tiyoesterase 1 (PPT1) gene. This mutation has not been shown in another case in literature.

P270
HALLERVORDEN-SPATZ CASE REPORT "CASE REPORT"

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Hallervorden-Spatz disease is a neurodegenerative disorder associated with cysteine-iron complex accumulation typically seen as bilateral symmetrical hypointense signal changes in the medial globus pallidus on magnetic resonance imaging. Both familial and sporadic cases have been reported.

A 5-year-old boy presented with a 2 year history of abnormal flexor posturing of the right hand and wrist with clenching of the fist, abnormal speech, attention deficit and ataxic walking. His developmental milestones were delayed and speech was slurred with inability to speak difficult words. Over 6 months it became fixed and persistent and also involved the left hand. Subsequently, he developed extension of the neck and flexion of the trunk, with grimacing of the face, tight closure of the mouth and deterioration of speech and walking. He was the product of a non-consanguineous marriage and was born at 34 weeks gestations. MRI showed hypointensity on T1 weighted imaging in both globus pallidi and an area of central hyperintensity ("eye-of-the-tiger"-sign) in both globus pallidi on T2 weighted imaging. After the MRI findings, the cytogenetic analyse done and, it showed, c.628+2T>G (homozygote). This mutation hasn't been defined before, so it should be valuable in diagnosing Hallervorden-Spatz patients.

P271
AN INFREQUENT NEURORADIOLOGICAL FINDING IN MENKES DISEASE

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BACKGROUND: Menkes disease is a relatively rare X-linked neurodegenerative disorder of copper transport secondary to mutations in the ATP7A gene. Grey and white matter abnormalities and spontaneous intracranial bleeding are well documented radiological findings. However, lactate peak on magnetic resonance spectroscopy (MRS) is less frequently described. This is commonly observed in a range of metabolic disorders typically mitochondrial diseases. When reported in Menkes disease, it is thought to result from energy failure due to deficiency of copper-containing enzymes.

AIM: To describe an infrequent finding on MRS in an unusual case of Meknes disease. CASE REPORT: This ex 29-week preterm boy presented at the corrected age of two months with episodes of hypothermia, lethargy and poor feeding. He had a difficult early neonatal course complicated by episodes of sepsis and hypothermia. During this presentation, he had episodes of tonic posturing and unresponsiveness that subsequently led to mechanical ventilation. Maintaining his body temperature within normal limits was difficult. Interestingly, he had very little body hair. A brain MRI scan demonstrated bifrontal chronic subdural haemorrhages, white matter loss and delayed myelination. MRS revealed a positive lactate peak in both basal ganglia and white matter. Both plasma and CSF lactate levels were normal. Plasma copper and caeruloplasmin were markedly low. A missense mutation in the ATP7A gene was found.

DISCUSSION & CONCLUSION: The differential diagnosis of a lactate peak on MRS in a male infant presenting with unusual neurologic manifestations should be expanded to include Menkes disease.

P272
LEUKOENCEPHALOPATHY IS A COMMON FINDING IN CHILDHOOD ONSET MITOCHONDRIAL DISEASE?

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Neuroimaging plays a vital role in the diagnosis of mitochondrial neurological disease. Grey matter abnormalities and stroke-like lesions are considered to be signature findings. We report the findings of children with white matter involvement or leukoencephalopathy in a cohort of children with suspected mitochondrial neurological disease.

Aim: To establish the frequency of white matter changes on neuroimaging in a cohort of children with suspected mitochondrial disease.

Method: Retrospective review of children with suspected mitochondrial neurological disorder over a 6 year period (April 2007 to 2013). We collected clinical, neuroimaging, biochemical and molecular genetic data.

Results: In the cohort of 108 children with suspected mitochondrial neurological disease, 54 (50%) had multisystem involvement; ophthalmoplegia and cardiac involvement are common comorbidities.

47 (43.5%) had predominantly white matter disease on neuroimaging, consisting of high T2 signal of deep cerebral and periventricular white matter. 30/47 (63%) had isolated white matter changes, 12/47 (25%) had white matter and basal ganglia changes and 5/47 (10%) had atrophy and abnormal white matter.

In the mitochondrial leukoencephalopathy group, a molecular genetic diagnosis was obtained in 40%, 19/47 (17 nuclear, 2 mitochondrial DNA mutations). In the 28 children without a molecular genetic diagnosis, 17/28 (60%) had abnormal respiratory chain in muscle, 2/28 abnormal muscle histology, 6/9 raised CSF lactate and 7/25 raised plasma lactate.

Conclusion: In our cohort of suspected mitochondrial disorders, leukoencephalopathy is common. The finding of leukoencephalopathy in a child with neurological and multisystem involvement should prompt a thorough evaluation for mitochondrial disease.

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EFFECT OF MIGLUSTAT ON NEUROLOGICAL OUTCOME IN EARLY INFANTILE NIEMANN PICK C

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Miglustat, a small iminosugar with its ability to cross the blood brain barrier has proved disease-modifying benefit on neurological manifestations in Niemann Pick type C1 (NPC1). We report the benefit of early use of this drug in infantile onset NPC1.

Case report: A female infant presented with neonatal cholestasis and hepatosplenomegaly and was diagnosed with NPC1. Her previous affected male sibling had early onset NPC1 with similar presentation. He was in a vegetative state by 4 years and died aged six.

She was started on Miglustat at 5 months of age after cholestasis resolved. At 30 months of age, her Niemann Pick disease related disability score was 4 with normal ambulation, manipulation, language and swallowing.

Development assessment at 3 years of age using Bailey scales showed a cognitive age of 19 months and gross motor age of 1 year. At 4 years of age she is able to run and climb onto furniture, she remains neurologically stable and continues to make developmental progress with no signs of regression.

Discussion: Early treatment with Miglustat significantly altered the disease course in this patient compared with the sibling, highlighting the importance of early diagnosis of neurological disease in NPC1.

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ASSOCIATION OF DERMAL MELANOCYTOSIS WITH GM1-GANGLIOSIDOSIS TYPE 1

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Introduction: Lysosomal storage disorders (LSD) are characterized by the accumulation of partially degraded insoluble metabolites within lysosomes. GM1-gangliosidosis type 1 is a hereditary deficiency of lysosomal acid beta-galactosidase, particularly severe entity with marked central nervous system involvement. Facial dysmorphism, hepatosplenomegaly, and generalized skeletal dysplasia are usually present in infantile cases. Dermal melanocytosis encompasses a clinical spectrum of cutaneous diseases such as Mongolian spots among others. The association of dermal melanocytosis with LSD is uncommon and still poorly understood. We report here a case of dermal melanocytosis associated with GM1-gangliosidosis type 1.

Patient: A 9-month-old Caucasian boy referred for evaluation of severe generalized hypotonia, lethargy and developmental delay. Extensive and unusual blue macules resembling Mongolian spots with larger lesions distributed over posterior trunk and axilla were found. In addition to the skin lesions, the infant had coarse facial features with low nasal bridge, broad nose, long philtrum; gingival hypertrophy, hepatomegaly, bilateral hydrocele and lumbar cyphosis also were found. Blood count reveal vacuolated lymphocytes. Elevated urine oligosaccharides and beta galactosidase activity deficient confirm the diagnosis of GM1.

Discussion: In the appropriate clinical setting, an unusual presentation of dermal melanocytosis may be a cutaneous sign of an underlying LSD.

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NEWBORN SCREENING FOR X-LINKED ADRENOLEUKODYSTROPHY: A PILOT STUDY

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Introduction: Currently available therapies for X linked adrenoleukodystrophy (XALD) are successful when administrated to asymptomatic or minimally symptomatic patients. For this reason newborn screening (NBS) has been advocated to offer timely intervention. However, for a condition to be added to the Recommended Uniform Screening Panel (RUSP), one of the key elements is the demonstration of high performance of the screening test in a population-based pilot. In order to assess clinical validity and performance metrics of a high-throughput assay, we are conducting a prospective study of 100,000 anonymized newborn dried blood spots (DBS).

Methods: A two tier approach, analysis of C20- to C26-lysophosphatidylcholines (LPCs) in DBS by Flow Injection Analysis tandem mass spectrometry (FIAMS/MS) and, when abnormal, by Liquid Chromatography (LC-) MS/MS was used. Molecular genetic analysis of the ABCD1 gene was performed on those samples with abnormal MS/MS results.

Results: To date we analyzed 74,460 NBS samples. Following the two-tier approach, ten samples were submitted for ABCD1 testing. Of these, two were found to be hemizygote males and one a heterozygote female. No testing was performed to exclude other peroxisomal disorders in the remaining seven cases.

Conclusion/Discussion: These preliminary data prove feasibility of NBS for peroxisomal disorders to be feasible. They also confirm the incidence the disease (ca. 1:17,000 males). Upon completion of the study reference and disease ranges will be determined which will guide result interpretation and further improve NBS performance (http://www.clir-r4s.org/).