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OBJECTIVE: Describe clinical, biochemical and molecular aspects of GA1-patients assisted at present in our service. Emphasize the variable clinical presentations with at least two forms: acute and late-onset.
MATERIALS AND METHODS: 7 patients whose diagnosis was biochemically established through the measurement of urinary organic acid by GCMS, acylcarnitine profile, and serum carnitine (free and total) after clinical and neuroimaging (MRI) suspicion, are presented. Mutation analysis was confirmed by Sanger sequencing of gDNA. Treatment was started at diagnosis in all patients and continued until the age of 6 years. It consisted on a protein-restricted diet, supplemented with a special amino acid mixture and L-carnitine.
RESULTS: All patients were symptomatic during the first 2 years (4 to 22 months). 5 patients presented with severe early-onset encephalopathy during a febrile illness, and developed a dystonic dyskinetic tetraplegia. Two of them substantially improved on follow-up. MRI showed striatal changes, variable cortical atrophy and enlarged sylvian fissures.
The other 2 patients presented with non-specific symptoms (focal seizures) without neurological signs, and diagnosis was suspected after brain MRI showing enlarged sylvian fissures without striatal lesions, one of whom developed extensive white matter changes.
Only 2 patients presented with non-excretory biochemical phenotype.
Two patients were homozygous for the more frequent R402W mutation but presented with different phenotype.
DISCUSSION: Even though the small number of patients, they represent the wide clinical phenotype of GA1. The presence of macrocephaly and a correct MRI interpretation allowed the diagnosis in the oligosymptomatic forms.
Non-excretory patients need molecular diagnosis and demand an exhaustive acylcarnitines examination when low free-carnitine is present. No phenotype/genotype correlations were detected.

P-144 - ETHYLMALONIC ACID INDUCES BIOENERGETIC DYSFUNCTION IN RAT CEREBELLUM BY DISTURBING MITOCHONDRIAL SUCCINATE UPTAKE

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BACKGROUND: Ethylmalonic encephalopathy (EE) is a devastating neurometabolic disorder caused by mutations in the ETHE1 and biochemically characterized by ethylmalonic acid (EMA) accumulation. Individuals affected by EE present with chronic circulatory and gastrointestinal problems, and severe neurological symptoms, whose pathophysiology is not totally established. Therefore, we investigated the effects of EMA on mitochondrial bioenergetics and redox homeostasis in cerebellum of rats.
METHODS: Mitochondrial preparations or supernatants were prepared from cerebellum of 30-day-old Wistar rats and used for the evaluation of EMA effects (2.5-5 mM) on mitochondrial respiration (states 3, 4, respiratory control ratio and uncoupled state) and membrane potential, glutathione (GSH) concentrations, malondialdehyde (MDA) levels, and aconitase, citrate synthase and respiratory chain complex II activities.
RESULTS: Our results demonstrated that EMA decreased state 3, respiratory control ratio and uncoupled state in succinate-supported mitochondria. Inhibitory effects elicited by EMA on succinate-supported respiration were attenuated by nonselective permeabilization of the mitochondrial membrane, suggesting that succinate transport is impaired. We also verified that EMA dissipated mitochondrial membrane potential, which was prevented by cyclosporine A plus ADP and ruthenium red. EMA further decreased aconitase activity. However, MDA levels, GSH concentrations and citrate synthase activity were not altered by this organic acid.
DISCUSSION: Our findings indicate that EMA impairs mitochondrial succinate uptake and induces mitochondrial permeability transition in cerebellum. It is presumed that these pathomechanisms underlie the neurological dysfunction observed in EE.
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P-145 - INVESTIGATION OF THE ROLE OF C26: 0-LYSOPHOSPHATIDYLCHOLINE IN THE OXIDATIVE STRESS INDUCTION IN X-LINKED ADRENOLEUKODYSTROPHY

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INTRODUCTION: X-linked adrenoleukodystrophy (X-ALD) is caused by mutations in ABCD1 gene and is characterized by very long-chain fatty acids (VLCFA) accumulation. It is clinically heterogeneous, however male patients are at high-risk to develop adrenal insufficiency and/or cerebral demyelination. Since untreated adrenal insufficiency can be life-threatening and considering the possibility of cure when hematopoietic stem cell transplantation is performed in an early stage of the disease, prompt diagnosis is crucial for a good prognosis. Thus, an

increasing interest has arisen in the neonatal screening of X-ALD, which is possible through the analysis of C26: 0-lysophosphatidylcholine (C26: 0-LPC). Although a considerable number of studies has demonstrated the importance of this new biomarker for the diagnosis of X-ALD, its role in the pathophysiology of this disease has not been investigated.
OBJECTIVES: Considering that oxidative stress is a well described mechanism of damage in X-ALD, our objective was to investigate if this mechanism could be related with C26: 0-LPC accumulation in X-ALD patients.
MATERIALS AND METHODS: We measured blood C26: 0-LPC concentrations in five patients with X-ALD (2 children, one with CCER and the other with AMN; and 3 adult heterozygous women) by liquid cromatography tandem mass spectrometry. Oxidative stress was investigated in these patients through the measurement of the reactive species formation by the 2',7'-dichlorofluorescin oxidation assay (DCF) in plasma and by determination of plasma sulphydryl groups, whose reduction reflects protein oxidation.
RESULTS: Our results showed a significant increase of C26: 0-LPC in blood of X-ALD patients when compared with healthy controls of similar ages, being higher in the male X-ALD patients in relation to the X-ALD female carriers. We also verified a strong inverse correlation between plasma sulphydryl groups and C26: 0-LPC (r=-0,817, p=0,091) and a positive correlation between C26: 0-LPC and DCF (r=0,611, p=0,274).
CONCLUSIONS: The correlations verified in this study between oxidative stress parameters and C26: 0-LPC probably could be significant whether the number of analyzed patients was higher, which would make it possible to separate the patients according their phenotypes. Even so, preliminary data from this study suggest that C26: 0-LPC may be involved in the induction of oxidative imbalance in X-ALD, deserving further investigation.

P-146 - N-ACETYL-L-CYSTEINE, TROLOX, AND ROSUVASTATIN PROTECT GLIAL CELLS EXPOSED TO HEXACOSANOIC ACID AGAIST INFLAMMATION, LIPID PEROXIDATION AND NITRATIVE STRESS

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INTRODUCTION: X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder caused by disfunction of the ABCD1 gene, which encodes a peroxisomal protein responsible for the transport of the very long-chain fatty acids from the cytosol into the peroxisome, to undergo β-oxidation.The major accumulated saturated fatty acids are hexacosanoic acid (C26: 0) and tetracosanoic acid (C24: 0) in tissues and body fluids. Recent evidence shows that oxidative and nitrative stress seems to be related with pathophysiology of X-ALD and many studies are associating antioxidants as an adjuvant theraphy, since there is no completely satisfactory treatment for this neurogenetic disorder.
OBJECTIVES: Considering that glial cells are widely used in studies of protective mechanisms against neuronal oxidative stress, we investigated whether C26: 0, incorporated in a lecithin vesicle, was capable to induce oxidative/nitrative damages and inflammation to glial cells and if the compounds N-acetyl-l-cysteine (NAC), trolox (TRO), and rosuvastatin (RSV) were able to protect cells against C26: 0-induced damages.
MATERIALS AND METHODS: C26: 0 was incorporated in lecithin vesicle by sonication. Glial cells were clultured in DMEM and at confluence, the vesicles containing lecithin and C26: 0 were added. A pre-treatment was performed for 2h at 37°C with NAC (100 μM), RSV (5 μM), and TRO (75 μM). Supernatants were collected for analysis. IL-1β was measured by an Invitrogen ELISA kit, NO equivalents and isoprostanes was detected by a Cayman kit.
RESULTS: It was observed that glial cells exposed to C26: 0 presented increased NO levels, high IL-1β levels, and increased isoprostane levels, compared to native glial cells without C26: 0 exposures. Furthermore, NAC, TRO, and RSV were capable to mitigate these damages caused by the C26: 0 in glial cells.
DISCUSSION AND CONCLUSION: Our data demonstrate, for the first time in literature, that C26: 0, by itself, induced in glial cells culture: lipid peroxidation, nitrative stress and inflammation. Furthermore, we verified that NAC, TRO, and RSV were capable to attenuate damages caused by C26: 0 in glial cells. The ability of these compounds to exert protective effects in glial cell culture might be of relevance as an adjuvant treatment for X-ALD, since there is still no completely satisfactory therapy for this disorder.

P-147 - SITOSTEROLEMIA IN COSTA RICA: REPORT OF THE FIRST CASE

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INTRODUCTION: Sitosterolemia is a rare autosomal recessive disorder of lipid metabolism characterized by increased intestinal absorption and a decrease in the biliary