195-P

ANAPLEROTIC THERAPY FOR ADULT POLYGLUCOSAN BODY DISEASE (APBD) WITH GLYCOGEN BRANCHER ENZYME DEFICIENCY

Mochel F[1], Haller R.G.[2], Wallace M.[3], Lossos A.[4], Akman H.O.[5], Schiffmann R.[3]
[1]*INSERM, UMR 679, Hôpital La Salpêtrière, Paris, France*
[2]*Neuromuscular Center Institute, Dallas, United States*
[3]*Inst of Metab Dis, Baylor Res Inst, Dallas, United States*
[4]*Depart of Neurol, Hadassah Med Ctr, Jerusalem, Israel*
[5]*Depart Neurol, Columbia Uni Med Ctr, New York, United States*

APBD is a degenerative neurogenetic disorder that is often caused by glycogen brancher enzyme deficiency. It is therefore the adult form of glycogen storage disease type IV (GSD IV). There is currently no effective therapy and the pathogenesis of the disease is poorly understood. We identified indicators of energy deficiency such as symptomatic hypoglycemia in an APBD patient on submaximal exercise. Symptomatic hypoglycemia is known to occur in an animal model of GSD IV and in other glycogen storage diseases. We therefore hypothesized that (i) decreased glycogen degradation leads to energy deficit in neurons and glial cells; (ii) anaplerotic therapy using triheptanoin, a 7-carbon triglyceride, will supply needed substrate to the citric acid cycle to correct the energy deficit and thus slow, halt or reverse the progression of the disease. Open label trial at a triheptanoin dose of 1–2 g/kg of body weight/24 hours showed a mean improvement of 10% in the 6-minute walk test over a mean follow up of 8.5 months (n=5, p=0.06). One patient had a 126 feet improvement (9.5%) at the 25 months time point. Physical Function score increased in 4/5 patients on the SF-36 health survey questionnaire. We consequently initiated a randomized controlled study in 18 subjects ingesting a diet supplemented with triheptanoin or a control long chain vegetable oil. Outcome measures include 6-minute walk test, motion capture gait analysis and quality of life. Should this therapeutic approach be successful, it may also be applied to other glycogen storage disorders.

196-P

RETROSPECTIVE EVALUATION OF CLINICAL PRACTICE: USING A MODIFIED STARCH IN THE MANAGEMENT OF GLYCOGEN STORAGE DISEASE

Mullally M[1], Mundy H[2], Champion M[2], Gick J[2], Eardley J[2], Emery P[1]
[1]*King's College London, London, United Kingdom*
[2]*Dept of IMD, Evelina Child Hosp GSTT, London, United Kingdom*

Background: Cornstarch therapy has been the mainstay of treatment for Glycogen storage disease for over two decades. Recent cross over trials of a modified cornstarch (Glycosade) have demonstrated improved fasting times and short term metabolic control. Longer term studies have not yet been reported.

Objectives: To compare the use of Glycosade as part of a standard dietary regimen in the longer term in 11 Glycogen storage disease patients (Type Ia, Ib and III) vs traditional uncooked cornstarch therapy / Evaluating fasting tolerance, height and weight, appetite and secondary metabolites

Methods: Glycogen storage disease patients under care of the Evelina Children's hospital (Type Ia, Ib and III) aged 3–18 yrs taking cornstarch as part of their dietary management were included in the service evaluation. Data from starch loading tests and clinic reviews were collated from electronic patient records, medical and dietetics notes

Conclusion: Overall median fasting tolerance was 6 hrs on UCCS and 8 hrs on Glycosade. Most of the effect was observed in Type Ia. There were no remarkable improvements in growth; however 3 patients reduced their weight. 5 out of 9 patients who changed to Glycosade reported improvements in appetite. The lactate profiles of Type I patients taking Glycosade revealed higher mean profiles ≥ 4 hours fasting compared to UCCS. However in Type III patients fasting free fatty acids were comparable using both starches.

197-P

IMPROVING GALACTOSEMIA SCREENING BY DECREASING THE FALSE POSITIVE RECALL RATE: THE SWEDISH EXPERIENCE

Ohlsson A[1], Guthenberg C[1], von Dobeln U[1]
[1]*Centre of Inherited Metabolic Diseases, Stockholm, Sweden*

Background: High rates of false positive cases of galactose-1-phosphate uridyltransferase deficiency (GALT-deficiency) are common in newborn screening programmes. This results in high costs for follow up and anxiety for parents. To minimize this we have developed a rapid, simple and cheap method to verify positive cases of classical galactosemia. All samples with less that 15% activity in the Beutler-test are tested for elevated galactose levels using the rapid GAL-DH-test. It is ready within an hour and the patients can thus still be recalled urgently.

Method: The rapid GAL-DH-test is a fluorometric assay where galactose can be approximated. Galactose dehydrogenase (GAL-DH) catalyses the oxidation of galactose and the reduction of NAD+ to NADH. The amount of NADH is proportional to the amount of galactose. The test is considered positive for galactose if NADH is produced, as demonstrated by fluorescence under ultraviolet light.

Results: In 1,522,291 screened newborns between the years 1992–2008, 22 newborns were recalled and 18 cases of GALT-deficiency were confirmed. No missed cases have been reported.

Conclusions: The rapid GAL-DH-test has been in use for almost 20 years at the Swedish newborn screening laboratory. Since the introduction of it in combination with a cut off value of less than 15% for the Beutler test we have had less than one false positive case for every true positive case of classical galactosemia. All confirmed cases have had an activity of less than 10% in the Beutler-test. This 2-tier approach gives a negligible false positive rate at a low cost.

198-P

TRANSALDOLASE DEFICIENCY: 4 NEW PATIENTS AND NEW PATHOPHYSIOLOGICAL INSIGHTS ON THE PENTOSE-PHOSPHATE PATHWAY

Valayannopoulos V[1], Rio M[2], Wamelink M[3], Rabier D[4], Ottolenghi C[4], Salomons G[3], Habes D[5], Jacqmain E[5], Bernard O[5], de Lonlay P[1], Jakobs C[3]
[1]*Ref Center IEM, Necker Enfants-Malades H, Paris, France*
[2]*Genetics Dep, Necker-Enfants Malades Hos, Paris, France*
[3]*Clin Chem Dep, VU Univ Med Center, Amsterdam, Netherlands*
[4]*Biochem Lab, Necker Enfants Malades Hosp, Paris, France*
[5]*Ped Hepatology, Bicetre Hosp, Le Kremlin-Bicêtre, France*

Background: Transaldolase deficiency, an inborn error of the pentose phosphate pathway has been diagnosed so far in 10 patients from 6 families. All presented as neonates, or even prenatally, with liver disease and the clinical courses have been diverse.

Patients: We present 4 new patients from 2 families of African origin. The 2 siblings from the first family presented with low birth weight, cutis laxa, anemia, thrombopenia, cholestasis, elevated transaminases and liver failure. The 2 siblings from the second family presented with hepatosplenomegaly, elevated transaminases and failure to thrive within the first months of life. All patients developed progressive liver failure and cirrhosis at various ages.

Methods and Results: Elevation of erythritol, arabitol and ribitol, sedoheptulose and sedoheptulose-7 phosphate were found in all patients' urine. Enzyme studies and molecular investigations confirmed the diagnosis. In one patient, respiratory chain complex I deficiency was found in liver and fibroblasts.

Conclusions: The new patients confirm that TALDO deficiency is panethnic and the constant hallmarks include liver impairment with cirrhosis associated to hematological abnormalities and abnormal polyols in urine. The respiratory chain findings in the liver of one of our patients may suggest novel mechanisms for liver damage in TALDO deficiency that has to be confirmed in other patients.