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of
INBORN ERRORS OF METABOLISM

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ABSTRACTS

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01. Inborn errors of metabolism in adult

O-001

Alteration of ornithine metabolism leads to dominant and recessive hereditary spastic paraplegia

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Background: *ALDH18A1* encodes delta-1-pyrroline-5-carboxylate synthase (P5CS), an enzyme that catalyzes the first and common step of proline and ornithine biosynthesis from glutamate. *ALDH18A1* mutations have been described 15 years ago in an autosomal recessive neurocutaneous syndrome comprising mental and growth retardation, cutis laxa, peripheral neuropathy and cataract.
Methods and results: Through exome sequencing, we report two families with autosomal recessive transmission of *ALDH18A1* mutations and predominant complex hereditary spastic paraplegia (HSP), marked cognitive impairment, but no cutaneous abnormality. More interestingly, we also identified monoallelic *ALDH18A1* mutations segregating in three independent families with autosomal dominant pure or complex HSP, as well as in two sporadic patients. Low levels of plasma ornithine, citrulline, arginine and proline in four individuals from two families suggested P5CS deficiency. In loading tests with ^{13}C labelled glutamine, P5CS flux was reduced in cultured fibroblasts from two affected subjects.
Discussion: Besides expanding the clinical spectrum of *ALDH18A1*-related pathology, we describe mutations segregating in an autosomal dominant pattern. We propose that the mechanism of pathology involves mitochondrial ornithine depletion. We suggest including plasma amino acid profiling as trait biomarkers in the work-up of HSP, particularly in dominant cases, as the associated phenotype is not distinct from other causative genes.

O-002

Does nitisinone in alkaptonuria alter non-metabolic outcomes? Experience from the United Kingdom National Alkaptonuria Centre

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Background: Nitisinone is used in treatment of alkaptonuria (AKU) at the National AKU Centre (NAC), Liverpool, UK. The resulting inhibition of p-hydroxyphenylpyruvate dioxygenase in the tyrosine degradation pathway results in decreased homogentisic acid (HGA) production. Nitisinone, so far, has not been shown to modify the evolution of AKU.
Patients and Methods: 38 AKU patients have attended the NAC, since 2012 (2 mg nitisinone daily). Eleven out of the 38 AKU patients also attended a non-interventional clinical study (2008-2011; mean follow-up of 36.8 months). AKU patients have completed one (n=26) and two (n=17) years of monitoring post-nitisinone with severity of AKU assessed by calculating the All AKUSSI scores allowing comparison pre- and post-nitisinone.
Results: **The** rate of change in AKUSSI was calculated and compared: these were 8±1.8 (pre-nitisinone), 1.2+1.4 (at one year), 1.3+1.0 (two years), with p values of < 0.001 only for the pre-nitisinone group. Plasma HGA showed a positive correlation with age (R 0.29; $p< 0.5$) and with All AKUSSI (R 0.44; $p< 0.002$) (Paired student's T test and Pearson's correlation coefficient).
Conclusion: The results are consistent with a decrease in evolution of AKU post-nitisinone therapy and this is the first data demonstrating a relationship between circulating HGA and the severity of AKU.

echocardiograms showed mild left-ventricular hypertrophic cardiomyopathy, with maximal wall thickness (MWT) of 12 mm and normal systolic function.In addition to obstetric care, she was seen once every trimester by metabolic and cardiologic team, showing stable parameters. Euglycemia was maintained throughout the labour by a dextrose infusion alone. Both infants were delivered vaginally at term, with an adequate weight for gestational age. Six months after the second childbirth, an increased cardiac MWT (20 mm) with stable ejection fraction was observed.
Conclusion: This case strengthens the evidence that a careful and suitable management strongly concurs to positive outcomes in GSD III pregnancies.

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Four patients with glycogen storage disease type 1b and Crohn's like colitis

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Background: Glycogen storage disease type Ib is an autosomal recessive disorder caused by defective translocase that transports glucose-6-phosphatase. Inflammatory bowel disease (Crohn's-like colitis) develops in those patients due to impaired neutrophil function and neutropenia.
Case Reports: Our report describes clinical and laboratory features of four patients with GSD Ib and Crohn's-like colitis. Three patients were two, four and five months of age; one patient was one day old. Two patients' molecular genetic analysis showed heterozygous mutation of G339C and homozygous mutation of C1211-2. Common findings were hepatomegaly, slightly elevated transaminases and triglyceride levels, lactic acidosis, hyperuricemia, and neutropenia. Liver biopsies were compatible with glycogen storage disease. During the follow-up, patients had abdominal pain, fever, diarrhea and perianal lesions. Colonoscopic findings and histopathological examinations of the biopsies showed active colitis and ileitis. All patients used immunosupression with corticosteroids and azathioprine. They are all in remission, and have been undergoing a combination of 5-ASA (5-aminosalicyclic acid), azathioprine and GCSF (Granulocyte colony-stimulating factor) treatments.
Conclusion: If patients with GSD1b have chronic diarrhea, anemia, fever of unknown origin, perianal and oral lesions, Crohn's-like colitis should be considered. GCSF with immunosupressive treatment improves neutropenia and the colitis in the patients.

P-297

A novel mutation in the *ABCC8* gene causing a variable phenotype of impaired glucose metabolism in the same family

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Background: Dominantly acting loss-of-function mutations in the *ABCC8* gene, encoding the SUR1 subunit of KATP channel, are usually responsible for mild diazoxide-responsive congenital hyperinsulinism (CHI). An increased risk of diabetes mellitus (DM) in adulthood has been suggested. The mechanism is not yet clear.
Case Presentation: The index patient was born at term to non consanguineous parents. Birth weight was 3900 g. Diagnosis of CHI was performed in the first week of life. The patient was started on diazoxide when he was 3 months as the drug was unavailable in his country. He showed a good response. A novel heterozygous *ABCC8* missense mutation (p.A478T) was found. F-DOPA PET/CT scanning was inconclusive.The patient's mother had gestational diabetes and after delivery she developed type 2 DM. The patient's grandfather developed type 2 DM at 45 years of age. Both had no past history of hypoglycaemia and were heterozygous for the p.A478T mutation.
Conclusion: The novel mutation identified in our patient was not previously reported in diazoxide-responsive forms of CHI; nevertheless a different mutation at the same residue has been reported in a family with CHI. The p.A478T *ABCC8* mutation seems to be associated to an incomplete penetrance of hypoglycaemia in infancy.

P-298

Ketogenic diet in congenital hyperinsulinism: a novel approach to prevent brain damage

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