083-O

IMPLICATION OF BIRTH COHORT, AGE AT ONSET, ENZYMATIC SUBGROUP AND COBALAMIN RESPONSIVENESS ON LONG-TERM OUTCOME IN ISOLATED METHYLMALONIC ACIDURIAS

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Background: Isolated methylmalonic acidurias (MMA) are caused by deficiency of methylmalonyl-CoA mutase (mut^0 or mut^- disease) or by defects in the synthesis of its cofactor 5′-deoxyadenosylcobalamin (cblA and cblB). The aim of this study was to evaluate the effects of birth cohort, presymptomatic diagnosis, age at onset, cobalamin responsiveness and enzymatic subgroup on long-term outcome as defined by survival, developmental delay, handicap and chronic renal failure (CRF).

Methods: Standardised questionnaires were sent to 17 European metabolic centres asking for biochemical and clinical outcome parameters. Data were evaluated using complex statistical models: Cox regression and partitioning, accelerated failure time model, logistic regression and proportional odds model.

Results: 244 patients were included. Neonatal onset of the disease was associated with high mortality, high incidence of developmental delay and severe handicap. Cobalamin non-responsive patients with neonatal onset who were born in the 70s and 80s had a particularly poor outcome. A more favourable outcome was found in patients with late onset of symptoms who were cobalamin responsive or were enzymatically classified as mut^- or cblA/B. Presymptomatic diagnosis was identified as possible protective factor concerning occurrence of handicap. Surprisingly,estimated cumulative distribution frequency of CRF did not show significant differences between enzymatic subgroups. However, CRF did manifest earlier in mut^0 patients.

Conclusions: Outcome in MMA is related to enzymatic subgroup, cobalamin responsiveness, age at onset and birth cohort. It remains unfavourable in patients with neonatal disease onset who are cobalamin-nonresposive, particularly mut^0 patients.

084-P

MUTATION IDENTIFICATION FOR TAIWANESE PATIENTS WITH ISOLATED METHYLMALONIC ACIDEMIA

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Background: Isolated methylmalonic academia (MMA) is an autosomal recessive disorder of organic acid metabolism caused by dysfunction of methylmalonyl CoA mutase (MCM, E.C.5.4.99.2; gene symbol: MUT) which requires adenosylcobalamin (Adocbl) as a cofactor. Defects in the MCM apoenzyme (mut type) or Adocbl synthesis (cblA type) may cause isolated MMA. **Methods**: Mutations in the MUT, MMAA and MMAB genes were determined in ten unrelated Taiwanese mut type MMA and one consanguineous B12-responsive MMA by PCR-based sequencing analysis. **Results**: Eight mutations in the MUT gene, designated c.316A>C (p.T106P), c.682C>T (p.R228X), c.919T>C (p.F307L), c.1280G>A (G427D), c.1630_1631GG>TA (G544X), c.1741C>T (R581X), c.755dupA (p.H252Qfs*6), and c.1561–1G>A, were identified in ten unrelated mut type patients. None of 100 alleles for 50 unrelated normal individuals were found to have these novel alterations. These data indicated that these alterations identified in Taiwanese patients might be disease-causing mutations in mut type MMA. The allele frequency of c.1280G>A mutations was 45% (9/20) in Taiwanese mut type MMA. The c.1280G>A mutation was linked to a 190 bp allele of a microsatellite marker D6S269. The allele frequency of 190 bp allele in Taiwnese mut MMA with c.1280G>A mutation was statistically different from that in the normal population. One c.742C>T (p.Q248X) mutation in the MMAA gene was identified in a B-12 responsive MMA from a consanguineous family. No alteration was found in the MMAB gene for this patient and thus confirm as a cblA type MMA. **Conclusions**: The c.1280G>A mutation is a common mutation in Taiwanese mut type MMA and might have founder effect.

085-P

3-HYDROXY-3-METHYLGLUTARIC ACIDURIA IN PORTUGUESE PATIENTS: CLINICAL, NEURORADIOLOGICAL AND GENETIC CHARACTERIZATION. A NEURODEGENERATIVE DISORDER?

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Background: 3-Hydroxy-3-methylglutaric aciduria (3HMG, OMIM 246450), is a rare autossomal recessive disorder caused by the deficiency of 3-hydroxy-3-methylglutaryl-CoA lyase (HL), affecting final step of leucine catabolic and ketogenic pathways. The HMGCL gene is located on chromosome 1p36.11. HL deficiency seems to be rare in Europe. Our experience suggests that is one of the most frequent organic aciduria in the Northern Portugal population.

Aim: to present/discuss the evolution of a 3HMG population.

Material: 10 patients, were identified in our unit, with variable clinical presentation; all had organic acid profile characteristic of 3HMG and enzymatic/molecular studies confirming diagnosis; two had fast fatal outcome (one late onset/one newborn screening diagnosis); from the remaining, six have a continuous follow-up in our centre. The main symptoms of clinical/ biochemical presentation were the usual. In all patients the same novel nonsense E37X mutation in exon 2 was found. During the follow-up (2–17 years) the patients had an apparent good control with usual approach without metabolic decompensations; all of them developed macrocephaly and in three patients insidious neurological deterioration was registered, with pyramidal/ extrapiramidal signs. The cerebral imaging showed progressive involvement along the years; all patients disclosed diffuse slightly hiperintense fronto-parietal white matter in T2W1 and DW1, sparing U fibers, with alterations in MRS, suggesting neuronal loss. Neurophysiological studies registered also alterations.

Conclusions: We emphasise a neurodegenerative aspects of HL deficiency that is suggested by the clinical follow-up and the evolution of the neurological studies in our patients. Larger population and accurate interpretation is needed.