Metabolic diseases

G209 DUAL PATHOLOGY IN TWO HYPOTONIC CHILDREN WITH PRADER-WILLI SYNDROME AND MUSCLE MITOCHONDRIAL COMPLEX I DEFICIENCY

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Aim & Method: To describe the features of two children with Prader-Willi Syndrome (PWS) and Complex-1 deficiency.

Results: Two children presented as neonates with hypotonia, feeding difficulties and growth retardation. Development was subsequently delayed. CPK, thyroid function, VLCFAs, ammonia and organic acids were normal. Serum lactate was normal in Case 1 and mildly elevated in Case 2. ABRs revealed delayed conductions of waves I-III. VEPs, EMG, NCS were normal. Neuroimaging showed mild cerebral volume loss. Muscle biopsy revealed a normal checkerboard pattern of Type I and II fibres and 1 mottled fibre (Gomori-trichrome staining) in Case I. Type II fibres predominated in Case 2. Mitochondrial stains for NADH, LDH, SDH and COX were normal. E/M revealed normal mitochondria and no lipid or glycogen accumulation. Mitochondrial enzyme analysis demonstrated unmeasurable NADH cytochrome-C-reductase activity in Case 1 and decreased activity of 11.7 nmol/min/mg mitochondrial protein (controls 94.6± 9.5) in Case 2. Succinate cytochrome-C-reductase activity was reduced in Case 2 at 47 (controls 102 ± 6.9) but normal in Case 1. COX activities were normal. In skin fibroblasts the lactate/pyruvate ratio was slightly elevated. The Prader-Willi phenotype became evident after 1 year of age. No deletion was detected in region 15q11-q13 with G-banding or FISH, however the methylation pattern was abnormal. Parental samples confirmed maternal uniparental heterodisomy of PWS.

Conclusion: The occurence of Complex-1 deficiency in PWS is likely a secondary rather than a primary event, but may contribute to the PWS clinical phenotype in certain cases.

G210 ARC SYNDROME IS NOT ALLELIC TO PFIC I AND II

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Introduction: ARC (arthrogryposis, renal dysfunction, cholestasis) syndrome, also known as Nezelof syndrome is a rare autosomal recessive metabolic disease. There have been less than 30 cases described in the literature over the last 30 years. The patients are born with variable degree of arthrogryposis, develop renal dysfunction in neonatal period, manifesting usually as proximal tubular insufficiency, and have persistent cholestasis. Liver biopsy displays features of giant cell hepatitis or biliary ductal hypoplasia. These findings are similar to those found in Progressive Familial Intrahepatic Cholestasis type I and II, which are characterised by a low gamma-glutamyl transpeptidase concentration, also present in ARC syndrome. We collected DNA from 12 families affected by ARC and investigated whether ARC is allelic with PFIC I or II.

Methods and Results: DNA from patients and their families were collected with informed consent. In total, 12 consanguineous families originating from Pakistan (5), Middle East (4), Italy (1) and Turkey (2) have been ascertained. Initial linkage studies were performed in four families using 4 fluorescent polymorphic markers which mapped close (within a genetic distance of 1 cM) of the PFIC I and II genes. Linkage to both genes was excluded in each family. We are now proceeding with a genome-wide linkage search to map the ARC locus.

Conclusions: ARC syndrome is not an allelic condition to PFIC I or II. Further research will help to identify a gene causing this devastating disease.

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G211 TRANSIENT NEONATAL CARNITINE DEFICIENCY: A POTENTIAL CAUSE OF NEONATAL COLLAPSE OR SUDDEN DEATH

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We describe four patients who presented in the first week of life with features consistent of a profound defect in fatty acid oxidation including hypoglycaemia, hyperammonaemia with mild ketosis, sudden infant death and tachyarrhythmias. On investigation they were found to have initial low carnitine levels that subsequently returned to normal without supplementation. They have remained symptom free with regards to any underlying inborn error of metabolism.

All four infants were born by Caesarean section and maternal carnitine levels were below or in the lower quartile of the normal range. Two had a history of poor feeding.

We hypothesise that transient carnitine deficiency may be a cause of neonatal collapse or sudden death. To our knowledge this has not previously been described.

G212 LATENT FAT OXIDATION DEFECT REVEALED ONLY ON DIAGNOSTIC FASTING

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A 17 month old boy, the first child of non-consanguineous parents, was referred with a 7 month history of chronic relapsing hepatitis. His younger asymptomatic sibling (aged 3 months) was also noted to have deranged liver function tests.

On two occasions, following a period of decreased oral intake, he developed encephalopathy with hypoglycaemia and deranged liver function. Alanine transaminase levels ranged between 358 and 2337 (normal 0-50 U/L). Liver histology showed inflammation with mild fatty changes. The creatine kinase was slightly elevated at 179 (normal 0-150 U/L). Clinically, he was not dysmorphic, with no organomegaly, jaundice, or signs of chronic liver disease. Development was age-appropriate.

On referral, when well, the plasma acylcarnitines, and organic acid profile were normal. However, on diagnostic fasting, hypoglycaemia occurred after 18 hours (glucose 1.9 mmol/L). Lactate remained normal throughout the fast. 3-hydroxybutyrate increased from 0.022 to 2.032 mmol/l while non-esterified fatty acids increased from 0.8 to 3.7 mEq/l indicative of a disorder of fat oxidation. The acylcarnitine profile was initially normal, but C14:1 increased to 0.86 µmol/L (normal <0.2) suggesting a diagnosis of very long acyl-CoA dehydrogenase (VLCAD) deficiency. However, fat oxidation studies in cultured fibroblasts showed normal oleate, palmitate and myristate oxidation.

We describe an unusual case of recurrent hypoglycaemic encephalopathy clinically and biochemically (*in vivo*) suggestive of VLCAD deficiency, but with normal fibroblast fat oxidation studies. Further biochemical and genetic investigation will be required to define the specific defect.

G213 HYPOGLYCAEMIA WITH LOW SUGAR DRINKS

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Background: High carbohydrate drinks are recommended for children during illness. Recently, use of low sugar drinks has increased due to dental concerns, with an increase in illness-associated hypoglycaemia.

Aim: To identify the frequency of low sugar drinks given during the preceding illness in children presented with hypoglycaemia.

Method: A review of non-diabetic children presenting with hypoglycaemia in A&E at Sheffield Children's Hospital between 01/01/99 and 31/07/02.

Results: 21 children (age 8 months to 5.2 years) had a blood glucose of <2.6mmol/L, range 0.8-2.6mmol/L, median 2.3 (ward based sugar-testing system). 20 had a short preceding illness (1-6 days). Hypoglycaemia was symptomatic in 7. Currently recommended blood

and urine investigations for possible underlying metabolic and endocrine disorder were undertaken in 16 before treatment. All responded to glucose given P.O. or I.V (subsequent blood glucose range 2.9-12.5, median 4.3). 18 were admitted. In 6 cases, only low sugar drinks were given during the illness. In addition 2 had artificial sweeteners in their urine. 8 with normal clinical examination, good lipolytic and ketogenic response and appropriate stress hormones levels were not investigated further, 7 were investigated later, 5 were lost to follow-up and 1 is under investigation. One had hyperinsulinism and 1 possibly a fatty oxidation defect. In 14 children "ketotic hypoglycaemia" was diagnosed (67%). They were discharged with advice or an "emergency regimen" for high carbohydrate drinks during illness. Clinic follow-up confirmed no further episodes of provoked hypoglycaemia.

Conclusions: Low blood sugar during illness in healthy children is rarely encountered outside "ketotic hypoglycaemia". At times of intercurrent illness when oral intake is compromised, 8/21 (38%) had been given low sugar or artificially sweetened drinks. We recommend that low sugar drinks are avoided during illness in young children.