Metabolic Disease

G216  RICKETS AT BIRTH ASSOCIATED WITH LOW BIRTH WEIGHT AND SUSPECTED RESISTANCE TO VITAMIN D

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Rickets is well known among low birth infants. 55% of infants <1000g and 23% < 1500g demonstrate radiological evidence of rickets, while 24% < 1500g have fractures. Inadequate dietary intake, rapid growth, end organ insensitivity, placental insufficiency, and poor absorption have all been implicated in the pathophysiology. Rickets of prematurity is most likely to occur in ELBW(<1000g). Most are asymptomatic and diagnosis is made radiologically. We describe the case of a male infant born at 34/40 by emergency LSCS weighing 1247g with clinical and radiological evidence of rickets at birth. Clinical features included craniofibro and rachitic rosary. Radiological investigations confirmed marked osteopaenia and multiple long bone fractures. Maternal investigations were all normal. The infant had evidence of chronic lung disease and necessitated diuretic therapy at 2/12. Initial investigations demonstrated a low normal serum calcium, low serum phosphate, high urinary calcium, normal urinary phosphate and raised alkaline phosphatase. Exogenous phosphate was prescribed. PTH levels were elevated with low 25-hydroxy vitamin D and grossly elevated levels of 1,25-hydroxy vitamin D. Serum levels of phosphate slowly returned to normal, but, other biochemical abnormalities persisted. Avitamin D receptor abnormality or end-organ resistance to vitamin D was suspected, therefore vitamin D therapy was commenced at 2/12.

Biochemical and radiological improvement was evident at 3 months of age. He continues to be followed. This case highlights the importance of early intervention for treatment of this common condition and some if the diagnostic difficulties associated.

G217  CREATININE EXCRETION IN CHILDREN TREATED WITH LOW PROTEIN DIETS FOR INBORN ERRORS OF METABOLISM (IEMS)

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Background: Urinary metabolite/creatinine ratios are frequently used to assess metabolic control in IEMs. Creatinine excretion may vary with protein intake, underlying condition, gender, age and body composition.

Aim: To investigate the variability of creatinine excretion with these factors.

Methods: 74 children (44 males, 30 females) (30 urea cycle disorders UCDs, 44 organic acidemias (OAs) donated 589 24 hour urine specimens for routine monitoring (15 patients gave one sample; 3 patients gave 20% of samples). Creatinine concentration and 24 hour excretion was measured by standard methods. Protein intake was assessed by dietary enquiry. The relationship between the above factors and creatinine excretion was analysed by least squares regression taking account of repeat sampling. Results are expressed as regression coefficients with 95% confidence intervals (CI) and by percent explained variation. Coefficient of variation (CV) was calculated for patients multiply sampled within the same week.

Results: Total explained variation was 73.1% with 64.4% explained by weight alone, with a 2.6% improvement when height was included; age was non-contributory. Males had significantly higher excretion (mean difference = 0.49 mmol/24 hr, 95% CI = 0.28,0.69. Patients with OAs had significantly lower excretion than UCDs (mean difference = 0.59 mmol/24 hr, 95% CI = -0.36,-0.81). There was a positive dose-response with protein intake. The CV ranged from 0 to 124%; 28.7% fell below 10% and 11.5% were above 50%.

Conclusions: Creatinine excretion depends on protein intake and disorder with wide inherent daily variation. There is need for caution in the interpretation of metabolite/creatinine ratios.

G218  CYTOCHROME C-OXIDASE DEFICIENCY—A VARIED CLINICAL SPECTRUM

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Aim and method: We studied the clinical spectrum of 13 children diagnosed with Cytochrome C-Oxidase (COX) deficiency at Birmingham Children’s Hospital between 1992 and 1999. Diagnosis was made with analysis of respiratory chain complexes in muscle tissue (open quadriceps biopsy).

Results: 1. Clinical presentation and progress
   Onset: 5 children presented in the neonatal period and 6 presented in the first year of life, often with a mild illness (viral upper respiratory tract infection).

   Common symptoms were: Respiratory distress (11), acute metabolic crisis (10), muscle hypotonia (8), developmental delay (6), hepatomegaly (6), epileptic seizures (5), encephalopathy (5), failure to thrive (5) and ophthalmoplegia.

   Other symptoms were: arthrogryposis (2), ataxia (1), nystagmus (1), dystonia (1), myopathy (1), cardiomyopathy (1) and macrocephaly (1). Usually a combination of symptoms was found in a patient.

   Progress: A transient form was found in 3 children. 3 children died in the neonatal period. 5 died before the age of five. 5 are alive at the ages of 1, 4, 5, 7 and 28 years. 2. Investigations

   Lactate: Serum levels ranged from 1.5 to 15.3 mmol/L, CSF levels ranged from 1.3–9.7.

   Biopsy: COX activity was decreased in both muscle and fibroblasts in 4 children.

   Mitochondrial DNA mutations: 1 child was heterozygote for SURF1 gene and 4 were homozygote.

Conclusion: COX deficiency has a wide range of symptoms and a varied progress.

G219  PROGRESSIVE DIFFUSE CEREBRAL DEGENERATION WITH LIVER DISEASE (ALPERS-HUTTENLOCHER DISEASE) IN ASSOCIATION WITH ADRENAL INSUFFICIENCY. A NEW ASSOCIATION?

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Alpers-Huttenlocher disease is characterised by diffuse cerebral degeneration and liver disease. It is probably heterogeneous, with some patients having a mitochondrial disorder. Adrenal insufficiency has not been reported in this disease.

We report three sisters with Alpers disease, two of whom presented with intractable epilepsy. The first died unexpectedly with liver failure aged 3 years. The second child died aged 4 years from intractable epilepsy. During the 2nd year she developed hypoglycaemia with generalised ischaemia and was found to have hypoadrenalism. Postmortem examination revealed liver disease and adrenal hypoplasia.

The surviving sister shows the neurological features of Alpers similar to her sisters, and is hyperpigmented. This child has functional hypoadrenalism demonstrated by cortisol profile and synacthen stimulation testing. Plasma very long chain fatty acids were normal.

We are not aware of an association between hypoadrenalism, progressive neurological deterioration and terminal liver disease. Antemortem muscle biopsy in the second child showed reduction in cytochrome oxidase complexes 1 and 4 suggesting a mitochondrial abnormality. We propose that the adrenal disorder in these children is due to a previously unrecognised effect of mitochondrial dysfunction on steroidogenesis.

Adrenal function testing and adrenal imaging should be considered in children with intractable progressive epilepsy, and hypoadrenalism considered in all mitochondrial disorders.