Neonatal inherited metabolic diseases

2008

Major classes

- Disorders of **carbohydrate** metabolism
  - E.g., glycogen storage disease, galactosaemia
- Disorders of **amino acid** metabolism and transport
  - E.g., phenylketonuria, branched-chain organic acidurias, glutaric acidemia type 1, urea cycle defects
- Disorders of **fatty acid oxidation** and **mitochondrial** metabolism
  - E.g., medium chain acyl dehydrogenase deficiency (glutaric acidemia type 2), Disorders of ketogenesis and ketolysis, diorders of pyruvate metabolism, defects of respiratory chains
- Disorders of **nucleic acid** and **heme** metabolism
  - E.g., acute intermittent porphyria, Lesch-Nyhan syndrome
- **Vitamin**-responsive disorders
  - E.g., Multiple carboxylase deficiency
- Disorders of **lipid** and **bile acid** metabolism
  - E.g., dyslipidaemias, disorders of bile-acid synthesis
- Disorders of **metal** transport
  - E.g., Menkes disease, acrodermatitis enteropathica
- **Organelle**-related disorders: lysosomes, peroxisomes and Golgi and pre-Golgi systems
  - E.g., lysosomal storage disorders, mucopolysaccharidosis, peroxisomal disoders, congenital defects of glycoxylation
- **Neurotransmitter** and **small peptide** disorders
  - E.g., Gaucher's disease (E75.22)

Disorders of carbohydrate metabolism
E.g., glycogen storage disease

PMH

- Glycogen storage diseases type Ib (4 X) ,type VI (1 X)

Other hospitals

- Type Ia
- Type II
- Galactosaemia

Disorders of amino acid metabolism

PMH

- Urea cycle defects: e.g. deficiency of OTC (4 x), Arginosuccinate lyase (2X), Citrullinaemia (1X)
- Sacrcosinaemia (3 X)
- Glutaric aciduria type I (2 X)
- Non-ketotic hyperglycinaemia

Other hospitals

- Maple syrup urine disease

Disorders of amino acid metabolism (organic acidurias)

PMH

- Methylmalonic aciduria (3 X)
- Methylmalonic aciduria with homocysteinuria (1 X)
- Isovaleric aciduria (1 X)

Other hospitals

- Propionic aciduria

Disorders of fatty acid oxidation and mitochondrial metabolism

- Carnitine acylycarnitine translocase deficiency (3 X)
- Glutaric aciduria type II (2 X)
- Beta-ketothiolase deficiency
- Mitochondrial cytopathy:

  MELAS (7 X)

  Kearns-Sayre snydrome

  Fanconi syndrome

Disorders of **nucleic acid** and **heme** metabolism

- Dihydropyrimidine dehydrogenase deficiency

Vitamin-responsive disorders

- Biotin-responsive multiple carboxylase deficiency

Disorders of **lipid** and **bile acid** metabolism

- Homozygous familial hypercholesterolaemia
- Apo C 2 deficiency (2 X)
- Sitosterolaemia (1X)

Lysosomal storage disorders

PMH

- Gaucher disease
- Mucopolysaccharidosis type I (3 X)
- Mucopolysaccharidosis type II (2 X)
- Niemann-Pick B disease
- GM1 gangliosidosis

Other hospitals

- Peroxisomal disorders
- MPS type IV and VI

Others

PMH

- Sulphite oxidase deficiency
- Citrin deficiency (2 X)

The Hong Kong Journal of Paediatrics 1989; 6:111-114

Atypical Cases of Ornithine Transcarbamylase Deficiency

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Summary A Chinese family with two affected males and two female carriers of ornithine transcarbamylase deficiency is reported. The illness ran a mild atypical course, and could be managed with low protein diet. Protein loading test for carrier detection was useful in this family.

CLINCAL AND LABORATORY OBSERVATIONS

Gaucher disease with pulmonary involvement in a 6-year-old girl: Report of resolution of radiographic abnormalities on increasing dose of imiglucerase

Shing Yan Robert Lee, MRCP(UK), Alex Wan Cheong Mak, MRCP(UK), Kwai Fun Huen, FRCP, Steven Tak Sum Lam, FRCP, and Chun Bong Chow, FRCPCH

We report resolution of ground-glass appearance in high-resolution computed tomography of chest in a 6-year-old girl who had Gaucher disease with pulmonary involvement. This radiographic abnormality, which developed during the course of enzyme replacement therapy at doses between 20 to 60 U/kg/2 weeks, resolved when the dose was increased to 100 U/kg/2 weeks. This case illustrates the importance of trial of escalating dosage in the face of failure of response at lower doses. (J Pediatr 2001;139:862–4)

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BRIEF REPORT

Mitochondrial DNA deletion in a girl with Fanconi's syndrome

Kam Ming Au · Shing Chi Lau · Yuen Fun Mak · Wai Ming Lai · Tat Chong Chow · Mo Lung Chen · Man Chun Chiu · Albert Yan Wo Chau

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Abstract We report a sporadic large-scale mitochondrial deletion in a paediatric patient with Fanconi's syndrome. Renal biopsy disclosed chronic interstitial nephritis. Ultrastructural examination of the renal tissue showed many giant atypical mitochondria. Histochemical stains revealed markedly reduced cytochrome *c* oxidase (COX). Genetic analysis disclosed a novel mitochondrial deletion of 7.3 kb in both peripheral blood and renal tissue. Mitochondrial diseases have heterogeneous clinical phenotypes; mutation analysis has proved to be an effective tool in confirming the diagnosis.

A Report of Two Families with Sarcosinaemia in Hong Kong and Revisiting the Pathogenetic Potential of Hypersarcosinaemia

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Abstract

Introduction: Sarcosinaemia is a rare metabolic disorder which has not been reported in Asia. Clinical Picture: The urine samples of 2 patients were screened as a routine metabolic screening offered for patients with mental retardation in our hospital. We used gas chromatography-mass spectrometry (GC-MS) which is capable of detecting abnormal pattern in amino acids and organic acids. Plasma sarcosine level was further quantified by GC-MS. The same methods were used in the investigations of asymptomatic family members. Urine examination by GC-MS revealed excessive amount of sarcosine in urine (normally undetectable) and their plasma sarcosine levels were raised. The 2 differential diagnoses of presence of sarcosine in urine – glutaric aciduria type II and folate deficiency – were ruled out by the absence of abnormal organic acids in the initial urine screen and by normal serum folate level respectively. Screening of the 2 families identified excessive sarcosine in urine in 2 siblings, one from each family. However, these 2 siblings of indexed patients thus identified have no neurological or developmental problem. Conclusion: Our finding was consistent with the notion that sarcosinaemia is a benign condition picked up coincidentally during screening for mental retardation.

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Key words: Gas chromatography-mass spectrometry, Hypersacosinaemia, Sarcosine, Sarcosine dehydrogenase

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Sitosterolaemia and xanthomatosis in a child

兒童患上食物固醇血症和黃瘤病

A 4-year-old boy presented with multiple tuberous xanthomata and a fasting plasma sterol concentration of 18.3 mmol/L, consisting primarily of cholesterol. Two months after changing from an unrestricted diet to a cholesterol-lowering diet, the plasma sterol concentration decreased to 4 mmol/L. Fasting plasma cholesterol levels for his father and mother were 7.3 mmol/L and 6.0 mmol/L, respectively. The degree and rapidity of the child's response to dietary control, together with the fasting cholesterol results of both parents suggested a diagnosis of sitosterolaemia. Gas chromatography and mass spectrometry of the patient's plasma sterol levels showed that the percentage of β-sitosterol was raised at 12.76%, as was campesterol (6.26%), and stigmasterol (0.71%), confirming the diagnosis of sitosterolaemia. The addition of cholestyramine 4 g/day to a low sterol diet maintained the plasma sterol concentration at 4 to 5 mmol/L, and gradual regression of the xanthoma was observed. These findings indicate that a diagnosis of sitosterolaemia, a treatable cause of premature atherosclerosis, should be considered in children with severe hypercholesterolaemia whose plasma cholesterol level is highly responsive to dietary manipulation.

一名四歲男童呈現多塊結節狀的黃瘤，其空腹時的血漿固醇濃度為18.3 mmol/L，主要為膽固醇。經過兩個月把飲食轉為低膽固醇後，病人的血漿固醇濃度減少至4 mmol/L。病人父母空腹時的血漿膽固醇水平分別是7.3 mmol/L和6.0 mmol/L。從病人對飲食控制反應的程度和速度，以及父母空腹時的膽固醇水平，可診斷病人患上食物固醇血症。此外，血漿固醇水平的氣體色譜分析和頻譜分析顯示，病人的β-食物固醇百分比升至12.76%，而菜油甾醇(6.26%)和豆固醇(0.71%)亦同時上昇，因而確定了食物固醇血症的診斷。自從把考來烯胺按每日4克的劑量加到病人的低固醇飲食後，血漿固醇濃度維持在4至5 mmol/L，而黃瘤亦逐漸消退。這些發現顯示，對於患有嚴重的高膽固醇血症，而血漿膽固醇水平對飲食控制高度敏感的兒童，應考慮食物固醇血症的診斷；這種血症屬於一種早期的動脈硬化，而此病本身是可以治療的。

CASE REPORT

Carnitine-acylcarnitine translocase deficiency in three neonates presenting with rapid deterioration and cardiac arrest

Robert SY Lee 李誠仁
CW Lam 林青雲
CK Lai 賴志剛
YP Yuen 袁月冰
KY Chan 陳國燕
CC Shek 石志超
Albert YW Chan 陳恩和
CB Chow 周鎮邦

We report on three Chinese neonates with carnitine-acylcarnitine translocase deficiency. They presented within the first 48 hours of life. Two neonates were found in cardiac arrest; one of them survived after resuscitation. The third neonate suddenly developed cardiorespiratory insufficiency and succumbed eventually. The clustering of three cases in 5 years suggests that carnitine-acylcarnitine translocase deficiency is not rare in our Chinese population. We advocate that investigation for metabolic diseases including carnitine-acylcarnitine translocase deficiency should be performed in cases of sudden infant death and unexplained abrupt clinical deterioration in the early neonatal period. Non-ketotic hypoglycaemia is an early clue. The mainstay of initial treatment is glucose infusion at a rate greater than 7 mg/kg/minute, which inhibits beta-oxidation of fatty acids (the defective enzymatic steps in carnitine-acylcarnitine translocase deficiency) and thus prevents the accumulation of toxic long-chain acylcarnitines.

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Diagnosis of dihydropyrimidine dehydrogenase deficiency in a neonate with thymine-uraciluria

胸腺嘧啶—尿嘧啶嬰兒中的二氫嘧脫氫胸缺乏

Dihydropyrimidine dehydrogenase deficiency is an inborn error of pyrimidine metabolism characterised by thymine-uraciluria, convulsive disorders and developmental delay in paediatric patients, and an increased risk of toxicity from 5-fluorouracil treatment. This report is of the first patient with dihydropyrimidine dehydrogenase deficiency diagnosed in Hong Kong. The patient was a 2-day-old male neonate of Pakistani origin who presented with convulsions. Diagnosis was made by gas chromatographic-mass spectrometric detection of thymine-uraciluria and by molecular detection of a G to A point mutation in a 5'-splicing site leading to skipping of exon 14 in the *DPYD* gene of chromosome location 1q22. The results showed that the patient and his mother were homozygous and the father heterozygous for the splice site mutation. The mother also had thymine-uraciluria but was clinically asymptomatic.

二氫嘧脫氫胸缺乏是一種先天性嘧啶新陳代謝缺陷，在小童患者中會呈現胸腺嘧啶—尿嘧啶、痙攣性紊亂和發育延遲的特徵，並會增加5-氟尿嘧啶治療的毒性。本報告報導在香港診斷的首名二氫嘧脫氫胸缺乏患者。患者是一名巴基斯坦籍的兩天大男嬰，求診時呈現抽搐徵狀。由胸腺嘧啶—尿嘧啶的氣相質譜探測，以及在5'-節點中G到A點轉變導致漏讀了染色體1q22位的*DPYD*基因中外顯子14。結果顯示患者對節點轉變，與他母親的是純合，而與他父親的是雜合。此外，診斷過程中發現患者的母親同樣有胸腺嘧啶—尿嘧啶，但並沒有出現臨床徵狀。

‘Normal’ Outcome

As expected

- Glycogen storage diseases type type Ib
- Glycogen storage disease type VI
- Sacrcosinaemia
- Citrin deficiency

Depending of types / Subtypes

- Gaucher disease
- MPS type I
- MPS type II
- Niemann Pick B

All depends ……..

- Isovaleric aciduria
- Glutaric aciduria type II
- Beta-ketothiolase deficiency
- Biotin responsive multiple carboxylase

Borderline outcome

- OTC deficiency
- Glutaric aciduria type I
- Methylmalonic aciduria
- Glutaric aciduria type II
- Mitochondrial cytopathy: MELAS
- MPS type I

Moderate to severe mental retardation

- OTC deficiency (2 died)
- Arginosuccinate lyase deficiency (All died)
- Citrullinaemia
- Non-ketotic hyperglycinaemia
- Methylmalonic aciduria with homocysteinuria
- Carnitine acylycarnitine translocase deficiency (2 died)
- Dihydropyrimidine dehydrogenase deficiency (died)
- GM1 gangliosidosis (died)
- MPS type II
- Sulphite oxidase deficiency
- Mitochondrial cytopathy: (some died)

  MELAS (7 X)

  Kearns-Sayre snydrome

  Fanconi syndrome

Referred from other hospitals

- CACT deficiency (from a private hospital)
- Homozygous familial hyprecholesterolaemia
- Arginosuccinate lyase (from 2 public hospitals
- OTC deficiency (from a public hospital)

Towards early laboratory diagnosis

- Isovaleric aciduria in Jan 2008:

  3 days for biochemical diagnosis
- OTC deficiency in June 2008:

  10 hours for genetic diagnosis

Towards better treatment: Piling up of a greater variety of drugs

- Biotin
- Carnitine IV and oral
- Hydroxycobalamin (instead of cyanocobalamin)
- Pyridoxine
- Riboflavin
- Arginine
- Sodium benzoate, sodium phenylbutyrate
- Glycine

Towards better treatment:

- Better collaboration: HKSIEM
- Availability of hemodialysis (from the ‘era’ of no treatment to ‘era’ of peritoneal dialysis and then now the ‘era’ of hemodialysis)

Neontal screening of inherited metabolic disease (using tendon mass spectrometry on day 2)

May not be able to pick up in time

- Urea cycle defects
- Carnitine acylycarnitine translocase deficiency

Probable diagnosis in time

- Urea cycle defects
- Sarcosinaemia
- Glutaric aciduria type I and type II
- Methylmalonic aciduria
- Methylmalonic aciduria with homocysteinuria
- Isovaleric aciduria
- Beta-ketothiolase deficiency
- Dihydropyrimidine dehydrogenase deficiency
- Biotin-responsive multiple carboxylase deficiency

Neontal screening of inherited metabolic disease (using tendon mass spectrometry on day 2)

Unable to pick up

- Glycogen storage diseases
- Apo C 2 deficiency, Sitosterolaemia
- Sulphite oxidase deficiency
- Lysosomal storage disease or peroxisomal disorders
- Mitochondrial cytopathy:

  MELAS (7 X)

  Kearns-Sayre snydrome

  Fanconi syndrome