

Case Report

The First Case of Homocystinuria Picked Up by Newborn Screening in Hong Kong: A Case Report

S Ho, J Hui

Abstract Classical homocystinuria is a rare metabolic disease among the local Chinese population. We report a case of pyridoxine non-responsive classical homocystinuria who was picked up by the Hong Kong government's territory wide newborn screening programme which was started in 2015.

Key words Cystathionine beta-synthase deficiency; Homocystinuria; Newborn screening; Pyridoxine unresponsive

Introduction

The success of the pilot newborn screening (NBS) programme conducted between October 2015 and March 2017 in two public obstetric units encouraged the extension of the programme to cover newborn babies born in all the public obstetric units in Hong Kong. The programme screened for 24 metabolic conditions. In this case report, we report the clinical course of a newborn baby who was flagged as a possible case of homocystinuria with elevated methionine level and was subsequently confirmed to have classical homocystinuria.

Case Report

The proband was the firstborn of a non-consanguineous Chinese couple who enjoyed good past health. There was

no significant family history of note. She was born at 40 weeks of gestation after an uncomplicated antenatal course with a birth weight of 3.1 kg. Her first newborn screening at 48 hours of life showed an elevated methionine (Met) level of 84.8 $\mu\text{mol/L}$ (reference range [RR] 11-32 $\mu\text{mol/L}$). Both methionine-to-phenylalanine (Met/Phe) ratio and methionine-to-sum of the isobaric amino acids leucine, isoleucine, hydroxyproline (Met/XIe) ratio were elevated at 1.44 (RR 0.22-0.51) and 0.77 (RR 0.1-0.32) respectively. Repeated screening on day 5 showed further elevation of Met to 214 $\mu\text{mol/L}$ (RR 8-26 $\mu\text{mol/L}$). The baby remained asymptomatic all along with normal physical examination. Further workup confirmed an elevated methionine level of 292 $\mu\text{mol/L}$ (RR 10-60 $\mu\text{mol/L}$) on the plasma amino acid profile and total homocysteine (Hcy) level was significantly elevated to 150.4 $\mu\text{mol/L}$ (RR 2.9-10 $\mu\text{mol/L}$). Molecular genetic study by Sanger sequencing identified two novel compound heterozygous likely pathogenic mutations at c.439T>A p.(Ser147Thr) and c.912A>C p.(Glu304Asp) in the Cystathionine beta-synthase CBS gene. Both parents are heterozygous carriers of the CBS variants. These novel missense variants are classified as likely pathogenic according to the American College of Medical Genetics guideline as they exist in trans, are absent from the Genome Aggregation Database and predictions using multiple algorithms showed that both variants are pathogenic consistently. The proband was initially treated with pyridoxine and folic acid. Despite increasing to a high dose of 100 mg/day pyridoxine for a total of 3 weeks, there was no appreciable drop in the total homocysteine level. Upon the lack of response to the

Clinical Genetic Service, Department of Health, Hong Kong SAR, China

S Ho (何嘉倫) MBChb, MRCPCH, FRCPH

Metabolic Medicine, Hong Kong Children's Hospital, 1 Shing Cheong Road, Kowloon Bay, Kowloon, Hong Kong SAR, China

J Hui (許鍾妮) MBBS(NSW), MRCP(UK), FHKAM(Paediatrics)

Correspondence to: Dr S Ho

Email: stephanie_kl_ho@dh.gov.hk

Received June 11, 2019

medical treatment, the baby was started on a low methionine diet as prepared by mixing methionine-free and normal formula. Her methionine tolerance was gradually worked out through regular monitoring of the plasma total homocysteine and methionine levels. The patient was last seen at follow up at 18 months of age. She enjoyed normal growth and development.

Discussion

Classical homocystinuria (MIM 236200), otherwise known as Cystathionine beta-synthase deficiency is a methionine catabolic pathway disorder with variable prevalence amongst different ethnic backgrounds. It is most commonly reported in Qatar with a frequency up to 1:1800 but is considered exceedingly rare in the Chinese population.¹ Homocysteine (Hcy) is a non-structural amino acid produced during the catabolism of methionine. Hcy will be further converted into cystathionine with the help of the enzyme Cystathionine beta-synthase (CBS). In classical homocystinuria, the absence of CBS leads to an ineffective Hcy conversion resulting in methionine and homocysteine accumulation.

Classical homocystinuria is a clinically heterogeneous condition. It mainly manifests with problems in the eyes, and skeletal, central nervous and vascular systems. As patients can present to different specialists for their clinical problems, diagnosis is often delayed.² Clinical features include ectopia lentis, severe myopia, Marfanoid habitus, osteoporosis, bony deformities, thromboembolism, developmental delay, intellectual disability, seizure, psychiatric and behavioural problems. Great variations exist in terms of the age of onset, symptoms and progression of the disease. While some of the affected individuals can present in childhood with severe multisystemic disease, others remain asymptomatic throughout life. The phenotypical diversity may be partly related to the degree of pyridoxine-responsiveness although the exact pathophysiology of classical homocystinuria is yet to be fully understood. Mildly affected patients may present as adults with thromboembolism and are likely to respond to treatment with pyridoxine. The pyridoxine responsive patients could attain a normal homocysteine level after a small amount of pyridoxine supplementation. The largest cohort reported by far suggested only 44% of CBS deficiency patients are pyridoxine-sensitive.³ However as some of the individuals with pyridoxine-sensitive disease

may remain asymptomatic, this mild spectrum of the disease might be considerably underdiagnosed.³ In contrast, the more severely affected patients usually present in childhood with ectopia lentis, learning difficulties and skeletal abnormalities. These patients are usually managed with a low-methionine diet and/or betaine.² Early diagnosis is the key to reduce complications and long term morbidity among the affected patients. As symptomatic patients can present in a wide variety manner to a wide range of specialists including paediatricians, ophthalmologists, haematologists, neurologists, psychiatrists, orthopaedic surgeons, cardiologists, vascular specialists and clinical geneticists, it is very important that their symptoms be recognised and appropriate referrals and investigations follow.

The biochemical diagnosis of homocystinuria is made on the basis of an elevated plasma total homocysteine together with a high or borderline high level of plasma methionine. It is important to note that total homocysteine should be requested as a separate assay which is not routinely covered in the plasma amino acid profile. The availability of newborn screening enables homocystinuric patients to be picked up early and presymptomatically through an elevated methionine level on the dried blood spot cards. Majority of the individuals identified from newborn screening are subsequently proven to be pyridoxine unresponsive as is our patient. It is estimated that up to 50-80% of the homocystinuric patients picked up by newborn screening are pyridoxine unresponsive.^{4,5} Most pyridoxine unresponsive patients require a diet that is low in natural protein, with supplements of a Met-free special formula. This dietary treatment needs to be lifelong and is highly successful in preventing almost all the complications of classical homocystinuria, whilst maintaining normal growth and development.⁶

Without treatment, life expectancy is markedly reduced in patients with classical homocystinuria especially the pyridoxine unresponsive patients. When life-long treatment is started early in life, most patients are observed to have good outcomes. The importance of early detection by newborn screening cannot be overemphasised. It is hoped that with the implementation of a universal newborn screening programme, affected individuals could be diagnosed at the earliest instance and have a good prognosis and lead healthy and normal lives. Classical homocystinuria will then no longer be a cause of intellectual disability in our community.

Conflict of Interest

The authors declare they have no competing interest.

References

1. Zschocke J, Kebbewar M, Gan-Schreier H, et al. Molecular neonatal screening for homocystinuria in the Qatari population. *Hum Mutat* 2009;30:1021-2.
2. Morris AA, Koich V, Santra S, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. *J Inher Metab Dis* 2017;40:49-74.
3. Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet* 1985;37:1-31.
4. Naughten ER, Yap S, Mayne PD. Newborn screening for homocystinuria: Irish and world experience. *Eur J Pediatr* 1998;157(Suppl 2):S84-7.
5. Gan-Schreier H, Kebbewar M, Fang-Hoffmann J, et al. Newborn population screening for classic homocystinuria by determination of total homocysteine from Guthrie cards. *J Pediatr* 2010;156:427-32.
6. Walter JH, Wraith JE, White FJ, Bridge C, Till J. Strategies for the treatment of cystathionine beta-synthase deficiency: the experience of the Willink Biochemical Genetics Unit over the past 30 years. *Eur J Pediatr* 1998;157(Suppl 2):S71-6.