The first Saudi baby with classic homocystinuria diagnosed by universal newborn screening

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ABSTRACT

تعد البيلة هوموسيستينية الكلاسيكية (CH) خطأ فطري في التمثيل الغذائي ناتج عن نقص إنزيم سيستاثيونين بيتا سينثيز. يصاب المرضى المصابون بإعاقة ذهنية وأمراض مصاحبة أخرى. إذا تم تشخيصه مبكرًا في مرحلة الطفولة وبدأ العلاج، يحد من حدوث مضاعفات حتمية. يستخدم لفحص حديثي الولادة (NBS) مطياف الكتلة الترادفية (MSMS) لقياس مستويات الأحماض الأمينية. في CH، اختبار الفحص من الدرجة الأولى هو قياس الميثيونين بواسطة (MSMS). إذا ظل الميثيونين مرتفعًا في عينة الاسترجاع، فسيتم إجراء مستوى البلازما للهوموسيستئين. خضع رضيع حديث الولادة لقياس (NBS) روتيني في مركزنا والذي أظهر ارتفاع مستوى الميثيونين في العينة الأولى وعينة الاسترجاع. بعد ذلك، وجد أن إجمالي الهوموسيستئين في الدم مرتفعه، بما يتوافق مع تشخيص CH. بدأنا في العلاج الطبي والغذائي مبكراً لهذا الطفل السعودي الأول الذي تم تشخيصه بمرض بيلة الهوموسيستئين بمقياس (NBS) العالمي. يوضح هذا التقرير أن NBS لـ CH مجدية وفعالة في منع عبء المرض.

Classic homocystinuria (CH) is an inborn error of metabolism caused by cystathionine beta-synthase enzyme deficiency. Affected patients present with intellectual disability and other comorbidities. If diagnosed early in infancy and started treatment, inevitable complications can be prevented. Newborn screening (NBS) uses tandem mass-spectroscopy (MSMS) to measure the amino acid levels. In CH, the first-tier screening test is the measurement of methionine by MSMS. If methionine remained elevated in the recall sample, plasma level for homocysteine is performed. A newborn infant underwent routine NBS in our institute that showed elevated methionine in the first and the recall sample. Thereafter, total serum homocysteine was found to be elevated, consistent with the diagnosis of CH. An early medical and dietary management was commenced for this first Saudi baby diagnosed with homocystinuria by universal NBS. This report demonstrates that NBS for CH is feasible and effective in preventing the disease burden.

Keywords: CBS gene, homocystinuria, newborn, screening

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Classic homocystinuria (CH) is an inborn error of metabolism of sulfur amino acid, which is caused by cystathionine beta-synthase (CBS) deficiency (MIM#236200). Cystathionine beta-synthase enzyme catalyzes the first step of the transsulfuration pathway. Its deficiency results in elevated serum homocysteine and methionine. Classic homocystinuria is caused by different variants in the CBS gene.[1] Some patients present in childhood with multisystem disease, whereas others are asymptomatic into adulthood. The major clinical features are dislocation of the optic lenses, osteoporosis, 'marfanoid' habitus, learning difficulties, and thromboembolic events.[2] Patients diagnosed by newborn screening (NBS) do not exhibit the clinical manifestations of the disease at birth. Moreover, early diagnosis and treatment have been shown to prevent the complications of CH, including developmental delay.[3] The primary treatment strategy for CH is the introduction of a low methionine diet. Another therapeutic intervention is betaine therapy, which utilizes alternative pathways to reduce serum homocysteine. Increasing residual enzyme activity is entertained by using pyridoxine in patients with vitamin responsive

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variants.[4] Newborn screening for inherited metabolic disorders aims to detect patients before the symptoms and signs of diseases appear. The national NBS program in Saudi Arabia started in 2005. Currently, this program screens for 16 disorders, including different inborn errors of metabolism, congenital hypothyroidism, and congenital adrenal hyperplasia. Classic homocystinuria is not yet included in the national NBS program in Saudi Arabia. Nevertheless, the NBS in Prince Sultan Military Medical City (PSMMC) added CH to the existing disorders panel.[5] The prevalence of CH in Saudi Arabia is unknown. However, like other autosomal recessive metabolic disorders, CH is predicted to be prevalent in the consanguineous Saudi population.[6]

In this report, we describe the first Saudi patient with CH, who was diagnosed by universal NBS.

Case Report. *Clinical information.* The proband is a baby boy born at term with normal vaginal delivery weighing 3.5 kg, within the 50th centile chart. His clinical examination was unremarkable, including normal facial appearance, eyes, and central nervous system examination. The baby was commenced on bottle feeding. His parents are first cousins and have no family history of a genetic disease.

Diagnostic assessment. Newborn screening test was performed by taking a blood sample from his heel and analyzed by tandem mass spectroscopy (MSMS). The first NBS sample showed high methionine level 119 umol/l (normal: 8-75 umol/l) with methionine/phenylalanine ratio of 1 (normal is less than 1) (Table 1). The recall NBS sample showed higher methionine level, 146 umol, and higher ratio 1.9 consistent with possible CH. Then, his total plasma homocysteine was measured and found high at 204.4 umol/l (normal less than 10 umol/l), confirming the diagnosis of CH. The family was counseled regarding the diagnosis, the management plan, the prognosis, and the recurrence risk.

Therapeutic intervention. The baby was managed according to the CH guidelines that include starting low homocysteine special formula with restriction of natural protein intake. The medical treatment prescribed was intramuscular hydroxocobalamin injection 1 mg weekly, oral folic acid 2.5 mg daily, betaine 0.5 gram daily (dosage 100-150 mg/kg/day), and pyridoxine 40 mg twice a day. After one month of therapy, the total homocysteine was 1.50 umol/l (normal less than 10 umol/l). Timeflow was shown in Table 2.

Follow up and outcome. Whole exome sequencing revealed a homozygous pathogenic variant of CBS gene c.969G>A p. (Trp323*) that confirmed the diagnosis of CH at the molecular level (Figure 1). The baby was followed up by the medical and the dietetic team for one year. His growth and development were age-appropriate. His physical and eye examination was normal.

Table 1 - Biochemical and genetic characteristics of the patient with classic homocystinuria.

Test	Result	Reference range
Methionine (first sample)	119	8-75 micromol/L
Methionine (recall sample)	146	8-75 micromol/L
Methionine/Phenylalanine ratio (first sample)	1	Less than 1
Methionine/Phenylalanine ratio (recall sample)	1.9	Less than 1
Serum Homocysteine	204.4 micromol/liter	Less than 10
Molecular analysis	a homozygous pathogenic variant of cystathionine beta-synthase gene c.969G>A p.(Trp323*)	

Discussion. In this report, we present the first baby with classic homocystinuria diagnosed on routine newborn screening in Saudi Arabia. The national NBS program in Saudi Arabia started in 2005, with 15 disorders in the screening panel. These disorders include aminoacidopathies, organic aciduria, fatty acid

Table 2 - Timeline of the studied participant.

Event date	Clinical presentation	Diagnostic findings	Outcome and intervention
4 June 2019	Birth, asymptomatic	NBS, universal sample	High methionine , high homocystine to repeat NBS
8 June 2019	4 day old, asymptomatic	NBS recall	High methionine , high homocystine
8 June 2019	4 day old, asymptomatic	Dx: homocystinuria	Started on therapy and metabolic formula
16 July 2019	6 week old, asymptomatic	Whole exome sequencing	CBS mutation

NBS - newborn screening, CBS: cystathionine beta-synthase

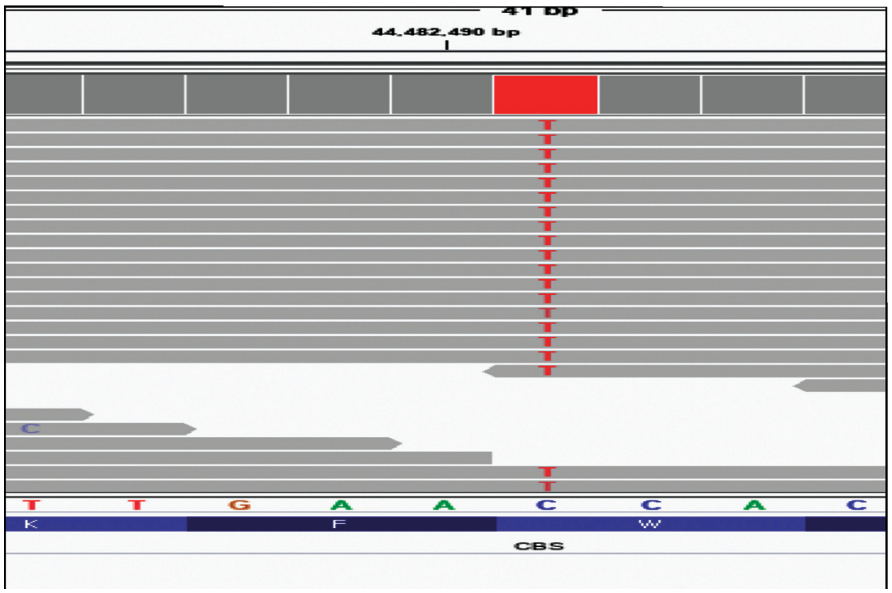

Figure 1 - Chromatograph of cystathionine beta-synthase gene showing a homozygous pathogenic variant.

oxidation defects, and 2 endocrine disorders, namely, congenital hypothyroidism, and congenital adrenal hyperplasia.[7] However, CH is not included in the national NBS program. The overall incidence of the screened diseases covered by the national NBS in Saudi Arabia between 2005 and 2012 was 1:1043, one of the highest incidence reported worldwide.[6] The incidence of IEM is higher than that observed globally which is to 50.9 per 100 000 live births.[7] This high incidence of genetic diseases in Saudi Arabia is caused by the high rate of consanguineous marriages in this country, which was estimated between 58%.[8] The patient reported in this study was born in Prince Sultan Military Medical City (PSMMC), a tertiary-level facility that serves the military personnel and their families. Our institute screens for the 17 disorders covered by the national NBS program; however, from January 2019, 3 diseases were added to the screening panel. These are CH, tyrosinemia, and primary carnitine deficiency.[5] Our patient was the first baby diagnosed by routine NBS since the introduction of CH screening in our hospital. Up to our knowledge, no other health care facility in Saudi Arabia currently screen for CH.

Most of the patients with CH in Saudi Arabia are diagnosed late. Zaidi et al[9] demonstrated this in 2011, who reported a case series of Saudi and Sudanese patients with CH who were diagnosed late and, therefore, mostly presented with complications including developmental delay, thromboembolism, skeletal deformity, and ectopia lentis.[9] Individuals with CH who were diagnosed in early infancy by NBS are expected to attain normal or nearly normal growth and development. Gan-Schreier et al[10] reported that over 3 years, a total of 14 patients with CH were diagnosed by NBS in Qatar; all had normal growth and development. This demonstrates that NBS for homocystinuria is feasible and effective. It prevents developmental delay, skeletal, and eye complications associated with CH.

In conclusion, we report the first baby diagnosed with CH by routine NBS. Including CH in the screened panel in the Saudi NBS is recommended to prevent the devastating disease burden associate with the late diagnosis of CH.

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