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

Talal AlAnzi, MD, Fahad J. Al Harbi, PhD, Joharah AlFaifi, MSc, Sarar Mohamed, FRCPCH, MD.

ABSTRACT

Tayyeb Al-Halbi, MD

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. 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. 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. 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.

Keywords: CBS gene, homocystinuria, newborn, screening

Saudi Med J 2021; Vol. 42 (2): 219-222
doi: 10.15537/smj.2021.2.25643

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.
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variants. 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. 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.

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.

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

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**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  | Less than 10    |
| Molecular analysis                  | a homozygous pathogenic variant of cystathionine beta-synthase gene c.969G>A p. (Trp323*) |

**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
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oxidation defects, and 2 endocrine disorders, namely, congenital hypothyroidism, and congenital adrenal hyperplasia. 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. The incidence of IEM is higher than that observed globally which is to 50.9 per 100 000 live births. 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%. 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. 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 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. 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 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.

References

1. Morris AA, Kožich V, Santra S, Andria G, Ben-Omran TI, Chakrapani AB, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. J Inherit Metab Dis 2017; 40: 49-74.
2. Moretti R, Caruso P. The controversial role of homocysteine in neurology: from labs to clinical practice. Int J Mol Sci 2019; 20: 231.
3. Voskoboeva E, Semyachkina A, Yablonskaya M, Nikolaeva E. Homocystinuria due to cystathionine beta-synthase (CBS) deficiency in Russia: Molecular and clinical characterization. Mol Genet Metab Rep 2017; 14: 47-54.
4. Kumar T, Sharma GS, Singh LR. Homocystinuria: Therapeutic approach. Clin Chim Acta 2016; 458: 55-62.
5. Mohamed S, Elsheikh W, Al-Aqeel AI, Alhashem AM, Alodaib A, Alahaideb L, et al. Incidence of newborn screening disorders among 56632 infants in Central Saudi Arabia. A 6-year study. Saudi Med J 2020; 41: 703-708.
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6. Alfadhel M, Al Othaim A, Al Saif S, Al Mutairi F, Alsayed M, Rahbeeni Z, et al. Expanded newborn screening program in Saudi Arabia: Incidence of screened disorders. *J Paediatr Child Health* 2017; 53: 585-591.

7. Walter D, Adeloye D, Woolham D, Westnedge E, Patel S, Rudan I. Global birth prevalence and mortality from inborn errors of metabolism: a systematic analysis of the evidence. *J Glob Health* 2018; 8: 021102.

8. Bener A, Mohammad R. Global distribution of consanguinity and their impact on complex diseases: Genetic disorders from an endogamous population. *Egypt J Med Hum Genet* 2017; 18: 315-320.

9. Zaidi SH, Faiyaz-Ul-Haque M, Shuaib T, Balobaid A, Rahbeeni Z, Abalkhail H, et al. Clinical and molecular findings of 13 families from Saudi Arabia and a family from Sudan with homocystinuria. *Clin Genet* 2012; 81: 563-570.

10. Gan-Schreier H, Kebbewar M, Fang-Hoffmann J, Wilrich J, Abdoh G, Ben-Omran T, et al. Newborn population screening for classic homocystinuria by determination of total homocysteine from Guthrie cards. *J Pediatr* 2010; 156: 427-432.