Scilight

International Journal of Clinical and Translational Medicine

https://www.sciltp.com/journals/ijctm

Case Report

Follow Up of Abnormal Newborn Screen for Homocysteine Metabolism—2 Case Reports

Ridwan B. Ibrahim [1,2], Nazmin Bithi [1,2], Adetoun A. Ejilemele [1,2] and Sridevi Devaraj [1,2,*]

[1] Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX 77030, USA
[2] Department of Pathology, Texas Children's Hospital, Houston, TX 77030, USA
* Correspondence: sxdevara@texaschildrens.org

How To Cite: Ibrahim, R.B.; Bithi, N.; Ejilemele, A.A. Follow Up of Abnormal Newborn Screen for Homocysteine Metabolism—2 Case Reports. *International Journal of Clinical and Translational Medicine* **2025**, *1*(3), 6. https://doi.org/10.53941/ijctm.2025.1000020.

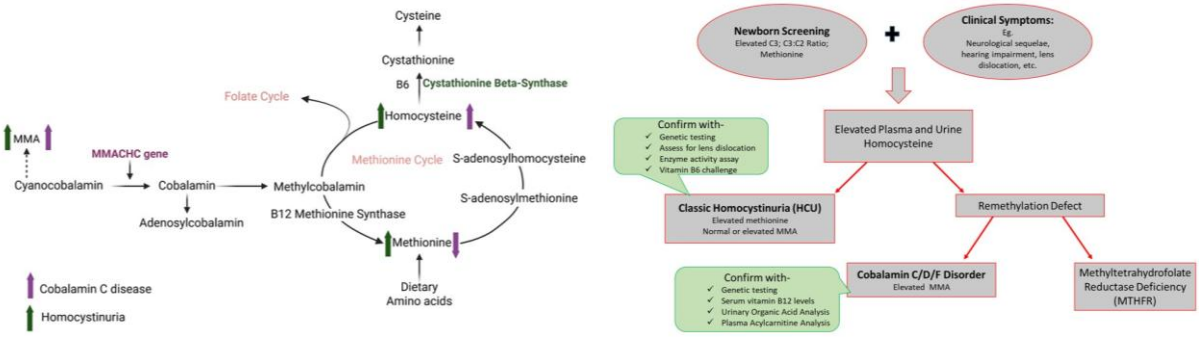
Received: 1 April 2025
Accepted: 22 April 2025
Published: 2 July 2025

Abstract: Two patients with abnormal newborn screens related to homocysteine metabolism are presented; one presenting with cobalamin c deficiency and the other with homocystinuria. These 2 case reports elucidate the workup for patients with homocysteine abnormalities following an abnormal newborn screen (NBS).

Keywords: homocysteine; cobalamin; newborn screen

1. Introduction

Cobalamin C disease (cblC) and isolated homocystinuria are metabolic disorders involving defects in the intracellular metabolism of cobalamin [1] and homocysteine respectively [2] (Figure 1). Homocystinuria is a condition inherited in an autosomal recessive pattern that prevents the body from processing protein correctly leading to elevated levels of methionine or homocysteine in the body [2]. There are different forms of homocystinuria, with the most common form in children being due to defective cystathionine beta-synthase (CBS) action which requires vitamin B6 as a cofactor to metabolize homocysteine into cysteine [2]. Cobalamin C disease on the other hand is an autosomal recessive inborn metabolic error caused by mutations in the metabolism of cobalamin associated C (MMACHC) gene resulting in impaired intracellular processing of vitamin B12 and consequently elevated methylmalonic acid (MMA) as well as homocysteine levels [3].



(a) (b)

Figure 1. (a) This diagram shows key pathways in homocysteine metabolism and highlights the effects of Cobalamin C (CblC) deficiency and classical homocystinuria.In the methionine cycle, dietary methionine is converted to S-adenosylmethionine (SAM),which donates methyl groups and becomes S-adenosylhomocysteine (SAH), eventually regenerating homocysteine. Homocysteine can also be converted to cystathionine via cystathionine beta-synthase (CBS), requiring vitamin B6. CBS deficiency leads to homocystinuria, with elevated homocysteine and methionine (green arrows). On the left, vitamin B12 (cyanocobalamin) is converted to active forms (methylcobalamin and adenosylcobalamin) through a process dependent on the MMACHC gene. In CblC deficiency, this conversion is impaired, disrupting both homocysteine remethylation and methylmalonic acid

(MMA) metabolism. As a result, homocysteine and MMA levels increase, while methionine decreases (purple arrows). **(b)** This flowchart outlines the diagnostic approach to elevated plasma and urine homocysteine detected through newborn screening or clinical symptoms (e.g., lens dislocation, neurological issues). Based on methionine and MMA levels, the chart differentiates between classic homocystinuria (Hcu), due to CBS deficiency, and remethylation defects, including cobalamin disorders and MTHFR deficiency. Confirmatory testing includes genetic analysis, enzyme assays, and vitamin/metabolite measurements..

Both disease conditions are characterized by abnormal homocysteine metabolism and can be identified early during newborn screens (NBS). The Texas NBS screen for metabolic disorders utilizes tandem mass spectrometry to analyze heel stick dried blood spot samples collected from newborns 24–48 h after birth with a second sample collected between 7–14 days of life [4].

Early diagnosis and prompt treatment of disorders of inborn errors of metabolism (IEM) is important to prevent permanent neurological damage [5,6]. Using two distinct cases, this case report describes the laboratory evaluation for both conditions.

2. Case Description

2.1. Case 1

A clinically well 3-week-old female with a normal first newborn screen presented to our hospital due to an abnormal second newborn screen significant for slightly elevated propionylcarnitine (C3). Her second screen was flagged as abnormal due to a borderline C3 level and an elevated C3/C2 ratio. She was admitted for further evaluation and to initiate therapy due to suspected cobalamin metabolism defect.

2.2. Case 2

A 4-week-old female was referred to our hospital for elevated methionine levels noted on second and third newborn screens. Total plasma homocysteine and methionine were elevated. There were no abnormalities noted on physical examination and her growth and development were progressing appropriately.

2.3. Laboratory Investigation

As with all abnormal screening results, confirmatory testing is required to confirm the presence of disease. For case 1, the recommendation was to measure urine organic acids, plasma acylcarnitine and plasma amino acids [7]. Patient's plasma amino acid results were normal with normal methionine levels, urine organic acid results showed elevated urine methylmalonic acid (MMA) level of 1992 (reference interval 0–5 mmol/mol creatinine) while plasma acylcarnitine results revealed elevated C3 (14.14 nmol/mL; reference interval < 0.94 nmol/mL). With elevated MMA, there are two possible broad differentials—methylmalonic aciduria or defects of cobalamin metabolism such as cobalamin C deficiency. To rule out methylmalonic aciduria, plasma homocysteine was measured. In classical methylmalonic aciduria, plasma homocysteine should be elevated with low methionine levels [8]. The patient's total plasma homocysteine was elevated at 82.1 µmol/L (reference interval < 10.4 µmol/L) with a normal methionine level making the differential for this patient likely to be cobalamin C deficiency. She was started on carnitine and hydroxycobalamin therapy while her buccal swab specimens was sent out for genetic testing. This identified biallelic variants c.331C>T (p.Arg111*) and c.482G>A (p.Arg161Gln) in *MMACHC*, consistent with a diagnosis of cobalamin C disease. She is continuously being managed with hydroxocobalamin and carnitine and is doing well with normal growth and development.

For case 2, the patient had hypermethioninemia on her NBS. For patients with elevated methionine on their newborn screens, the preferred investigation is to obtain plasma amino acids and plasma total homocysteine levels [7]. The patient's total plasma homocysteine and methionine were elevated at 85.9 µmol/L (reference interval 4–14) and 196 µmol/L (reference interval 9–45) respectively. Both of these findings were consistent with homocystinuria.

She was started on pyridoxine and folic acid while a blood sample was sent for genetic testing. A homozygous missense mutation c.1330G>A (p.D444N) on exon 14 of the cystathionine beta-synthase (CBS) gene which has been reported in patients with homocystinuria was identified [9]. Since B_6-responsive and B_6-non-responsive phenotypic variant of homocystinuria exist, a pyridoxine (B_6) challenge test was recommended to ascertain vitamin B_6 responsiveness [10]. Three weeks following pyridoxine and folic acid therapy, plasma levels of methionine and homocysteine were measured to confirm response to dietary therapy. Plasma levels of methionine and homocysteine remain elevated at 109.8 µmol/L (reference interval 11–50 µmol/L) and 133.3 µmol/L (reference

interval 4–14 μmol/L) respectively. The diagnosis was therefore redefined to non-B6 responsive homocystinuria. Subsequently, pyridoxine and folate were discontinued and she was placed on betaine plus methionine-restricted formula. Two weeks following the new diet regimen, plasma methionine returned to normal levels of 33.3 μmol/L (reference interval 11–50 μmol/L) while plasma homocysteine level decreased to 35.4 μmol/L (reference interval 4–14 μmol/L).

3. Discussion

CblC is the most common form of cobalaminopathies characterized biochemically by methylmalonic aciduria and hyperhomocysteinemia [11]. Clinical presentation is varied and affected individuals can present with symptoms at any age [12]. Homocystinuria is a rare autosomal recessive disorder associated with high total homocysteine levels and associated with clinical symptoms including developmental delay, ocular abnormalities, thromboembolic disease etc. [2]. Newborn screening programs have made early detection of these disorders possible. Following NBS, confirmatory testing is required to establish diagnosis. Homocysteine and methionine levels which can be measured in the clinical laboratory can allow early differentiation of both disorders. Table 1 and Figure 1a,b shows a typical workup to distinguish between CblC and homocystinuria following a positive NBS with expected changes in the levels of these analytes.

Table 1. Typical workup to distinguish between cobalamin C deficiency and homocystinuria.

	Cobalamin C Deficiency	**Homocystinuria**
Newborn screening	Elevated C3 Elevated C3/C2 ratio	Elevated methionine
Plasma homocysteine	Elevated	Elevated
Plasma methionine	Low or normal	Elevated
Methylmalonic acid	Elevated	Normal or mildly elevated

4. Conclusions

These cases highlight the critical role of newborn screening and focused metabolic evaluation in identifying and confirming inborn errors such as cobalamin C disease and homocystinuria. Prompt differentiation through biochemical and genetic testing enables early, targeted treatment while minimizing complications and optimizing developmental outcomes in affected infants.

Author Contributions

S.D.: conceptualization; R.I., N.B. : data curation, writing—original draft preparation; S.D.: supervision; A.E., S.D.: writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval were waived for this study, by Baylor College of Medicine Institutional Review Board due to only reporting less than 3 cases and using no unique identifiers.

Informed Consent Statement

Patient consent was waived due to above reason.

Data Availability Statement

Not applicable to this article. It is a case report.

Acknowledgments

Ridwan B Ibrahim and Nazmin Bithi are supported by the Ching-Nan Ou Endowment in Clinical Chemistry.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

References

1. Coelho, D.; Suormala, T.; Stucki, M.; et al. Gene identification for the cblD defect of vitamin B12 metabolism. *N. Engl. J. Med.* **2008**, *358*, 1454–1464. https://doi.org/10.1056/NEJMoa072200.
2. Gerrard, A.; Dawson, C. Homocystinuria diagnosis and management: It is not all classical. *J. Clin. Pathol.* **2022**, *75*, 744–750. https://doi.org/10.1136/jcp-2021-208029.
3. Martinelli, D.; Deodato, F.; Dionisi-Vici, C. Cobalamin C defect: Natural history, pathophysiology, and treatment. *J. Inherit. Metab. Dis.* **2011**, *34*, 127–135. https://doi.org/10.1007/s10545-010-9161-z.
4. Available online: https://www.dshs.texas.gov/sites/default/files/lab/PDF/NBS/Newborn-Screening-Laboratory-Brochure,-publication-14-14057.pdf (accessed on 14 April 2025).
5. Leonard, J.V.; Morris, A.A. Inborn errors of metabolism around time of birth. *Lancet* **2000**, *356*, 583–587. https://doi.org/10.1016/s0140-6736(00)02591-5.
6. Valayannopoulos, V.; Poll-The, B.T. Diagnostic work-up in acute conditions of inborn errors of metabolism and storage diseases. *Handb. Clin. Neurol.* **2013**, *113*, 1553–1562. https://doi.org/10.1016/B978-0-444-59565-2.00025-3.
7. American College of Medical Genetics and Genomics. *ACMG ACT Sheets and Algorithms*; American College of Medical Genetics and Genomics: Bethesda, MD, USA, 2001.
8. Baumgartner, M.R.; Hörster, F.; Dionisi-Vici, C.; et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. *Orphanet J. Rare Dis.* **2014**, *9*, 130. https://doi.org/10.1186/s13023-014-0130-8.
9. Kluijtmans, L.A.; Boers, G.H.; Stevens, E.M.; et al. Defective cystathionine beta-synthase regulation by S-adenosylmethionine in a partially pyridoxine responsive homocystinuria patient. *J. Clin. Investig.* **1996**, *98*, 285–289. https://doi.org/10.1172/jci118791.
10. Sacharow, S.J.; Picker, J.D.; Levy, H.L. Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency. In *GeneReviews(R)*; University of Washington: Seattle, WA, USA, 1993.
11. Weisfeld-Adams, J.D.; Morrissey, M.A.; Kirmse, B.M.; et al. Newborn screening and early biochemical follow-up in combined methylmalonic aciduria and homocystinuria, cblC type, and utility of methionine as a secondary screening analyte. *Mol. Genet. Metab.* **2010**, *99*, 116–123. https://doi.org/10.1016/j.ymgme.2009.09.008.
12. Wu, S.N.; E, H.S.; Yu, Y.; et al. Variable phenotypes and outcomes associated with the MMACHC c.482G > A mutation: Follow-up in a large CblC disease cohort. *World J. Pediatr.* **2024**, *20*, 848–858. https://doi.org/10.1007/s12519-023-00770-2.