Cross-Sectional Study

ANNALS OF MEDICINE & SURGERY

OPEN

Incidence and risk factors of ocular complications among patients with homocystinuria in Saudi Arabia: a cross-sectional study

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Background: Cysteine β-synthase deficiency, often known as classic homocystinuria, is an uncommon inborn mistake in methionine metabolism. Developmental delay, intellectual incapacity, skeletal and vascular symptoms, and ocular abnormalities are possible main clinical characteristics.
Objective: This study sought to describe the ocular anomalies that King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia, homocystinuria patients presented with between 2018 and 2022.
Methods: This retrospective research included six homocystinuria patients. Demographic and clinical characteristics of patients as age, gender, and comorbidities were collected. Relevant clinical and ophthalmic assessments, like visual acuity, fundus examination findings, complications, and type of surgery were also reported.
Results: Six patients with homocystinuria (12 eyes) were included. Associated diseases were mostly mental retardation (100%), epilepsy (66.7%), developmental delay (50.0%), scoliosis (33.3%), bronchiectasis (16.7%), thrombophilia (16.7%), metabolic disorders (16.7%), and deep venous thrombosis (16.7%). All patients had ectopia lentis (100%), while one patient (16.7%) had eye ectropion, one patient (16.7%) had anterior uveitis, and one patient (16.7%) had scleromalacia. Surgery type was mostly lensectomy and vitrectomy (83.3%) then scleral fixation (16.7%), and Grice green procedure (16.7%). There were insignificant differences between first and last Autoref readings in spherical, cylinder, and axis errors of right and left eyes
Conclusions: Late-diagnosed homocystinuria patients frequently have abnormalities of the eyes. Ectopia lentis should always raise the possibility that homocystinuria is the cause of the condition.

Keywords: classic homocystinuria, fundus photography scan, macular optical coherence tomography angiography, ocular complications, optical coherence tomography angiography, Saudi Arabia

Introduction

Classical homocystinuria (HCU) is a rare but life-threatening autosomal recessive metabolic disorder resulting in buildup of amino acid methionine and homocysteine in urine and blood due to cystathionine-β-synthase lack (CBS deficiency, OMIM 236200), which catalyzes the conversion of homocysteine to cystathionine[1]. Estimated global HCU prevalence is less than 0.38:100 000[2], and the etiology of CBS deficiency remains incompletely known. Apart from the build-up of homocysteine (Hcy), the abnormality also results in elevated levels of S-adenosyl homocysteine, improved remethylation to methionine, and reduction of cysteine and cystathionine[3]. Elevated Hcy amounts alter protein sulfhydryl groups and obstruct sulfhydryl group cross-linking in proteins like elastin, altering intracellular signaling and resulting in stress of endoplasmic reticulum and dysfunctional vascular endothelial cells[4]. Hyperhomocysteinemia, hypermethioninemia, and low cysteine levels are common in HCU patients[4,5].

HIGHLIGHTS

- All six patients with homocystinuria (HCU) included had ectopia lentis, while one patient had eye ectropion, one patient had anterior uveitis, and one patient had scleromalacia.
- Surgery treatment was mostly lensectomy and vitrectomy (83.3%) then scleral fixation (16.7%), and Grice green procedure (16.7%).
- Late-diagnosed HCU patients frequently have abnormalities of the eyes.
- Ectopia lentis should always raise the possibility that HCU is the cause of the condition.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2025) 87:2602–2607

Received 4 October 2024; Accepted 22 January 2025

Published online 7 February 2025

http://dx.doi.org/10.1097/MS9.0000000000003001

The prevalence of metabolic disorders is estimated to be highest in Saudi Arabia; this may be due to highest rate of consanguineous marriages among Saudi population[6]. The national newborn screening program in Saudi Arabia was established to detect metabolic disorders; and in 2019, homocystinuria was added to the panel. However; homocystinuria prevalence in Saudi Arabia is unknown[7,8].

Untreated cases lead to multisystemic problems as thromboembolic events, developmental delay, skeletal abnormalities, intellectual incapacity, and ophthalmic diseases[9]. The ocular and ophthalmic manifestations are unique and include ectopia lentis, high myopia, retinal detachment, degeneration, glaucoma, and others[1]. The main ocular feature associated with the disease is ectopia lentis that observed in 30% in infancy and tends to increase with age up to 80% in teenagers, and it is believed to be caused by decrease of disulfide-bonded C-terminal fibrillin-1 multimers[10]. Furthermore, it may progress in the late decade even with tight biochemical levels of amino acids[1]. Poor biochemical control and lens subluxation are associated with an increased risk of high myopia in homocystinuria patients. Zonular weakness, degeneration, and release of tension are thought to be the primary cause of high myopia which is diagnosed usually in the twenties[11,12]. The anterior motion of the lens and enhanced zonular dialysis are the main causes of pupillary block glaucoma[1]. Burke *et al* reported a 31% incidence of retinal detachment and degeneration among homocystinuria patients[13].

The effectiveness of pyridoxine treatment for HCU patients is determined by their response. Patients who respond well to the vitamin can maintain target levels of homocysteine (tHcy) while receiving it; non-responding patients need to be treated with betaine, low-natural-protein diets, and metabolic formulas without methionine[3].

This study aimed to describing ocular complications among homocystinuria disease patients at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia during the periods from 2018 to 2022.

Method

Study designs

An observational retrospective study was conducted in 2023 at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia. In order to determine the frequency of ocular problems among patients with homocystinuria at King Fahad Armed Forces Hospital in Jeddah, Saudi Arabia between January 2018 and December 2022, a cross-sectional approach was used in accordance with STROCSS 2021 standards[14]. The study was conducted an ethical approval based on the Declaration of Helsinki with registration research at the Health Research Ethics Committee of King Abdulaziz University (Approval # 2023-56, 16 August 2023). Informed written consent was obtained from all patients. Registration number of the study at ClinicalTrials.gov was NCT06545305.

Participants

Included criteria

All patients from all age groups who were diagnosed with homocystinuria between 2018 and 2022 were included, regardless of whether the diagnosis was made biochemically (by exhibiting hyperhomocysteinaemia and hypermethioninaemia) or genetically (by discovering biallelic pathogenic mutations in the CBS gene).

Excluded criteria

Patients with incomplete investigations for various reasons were excluded.

Data collections

The patient's records were collected from baseline outpatient internal medicine and pediatric encounters and had a past visit to ophthalmology clinic. Six patients in all met the criteria for study inclusion. A serial number rather than a medical record number was given to each trial participant in order to protect patient privacy. Most of the patients' data were sourced from their electronic medical files using a data collection sheet. The demographic and clinical characteristics of patients as age, gender, and comorbidities were collected. Relevant clinical and ophthalmic assessments, such as visual acuity, fundus examination findings, complications, and type of surgery were also obtained. Visual acuity, in-clinic dilated fundus examination, optical coherence tomography (OCT) angiography, macular OCT scan, and fundus photography were the main components of ophthalmic examinations. While the in-clinic dilated fundus examination involved retinal inspection with the use of mydriatic eye drops, visual acuity was measured using the tumbling E chart. Retinal disease-focused certified ophthalmology expert assessed the imaging results.

Statistical analysis

The values expressed as mean ± standard deviation (minimum-maximum) for normally distributed parametric data (demographic data) and median (25%–75%) for abnormally distributed parametric data (error of refraction) and frequency (%) for categorized data. Data were analyzed by Statistical Package for Social Sciences (IBM SPSS, IBM Corp., Armonk, NY, USA) version 22. The Shapiro–Wilk Test checked the normality of data distributions. Comparison between first and last Autoref reading was analyzed using Wilcoxon Signed Ranks test as parametric data were abnormally distributed. A P-value <0.05 was statistically significant.

Results

The female patients were more than male (83.3% vs. 16.7%). Patients ages ranged from 22 to 30 years with mean of 26.17 years. Age therapy commenced ranged from 3 to 11 years with mean of 8.33 years. Associated diseases were mostly mental retardation (100%), epilepsy (66.7%), developmental delay (50.0%), scoliosis (33.3%), bronchiectasis (16.7%), thrombophilia (16.7%), metabolic diseases (16.7%) and deep venous thrombosis (DVT) (16.7%) (Table 1).

All patients had ectopia lentis (100%), while one patient (16.7%) had eye ectropion, one patient (16.7%) had anterior uveitis, and one patient (16.7%) had scleromalacia. The type of surgery was mostly lensectomy and vitrectomy (n = 5, 83.3%) then scleral fixation (n = 1, 16.7%), and Grice green procedure

Table 1

Demographic and clinical characteristics of patients (n = 6).

Characteristics	Value
Gender	
Male	1 (16.7%)
Female	5 (83.3%)
Age (years)	26.17 ± 2.93 (22–30)
Age therapy commenced (years)	8.33 ± 3.01 (3–11)
Associated diseases	
Mental retardation	5 (83.3%)
Epilepsy	4 (66.7%)
Developmental delay	3 (50.0%)
Scoliosis	2 (33.3%)
Bronchiectasis	1 (16.7%)
Thrombophilia	1 (16.7%)
Metabolic diseases	1 (16.7%)
Deep venous thrombosis (DVT)	1 (16.7%)

(n = 1, 16.7%) (Table 2). Lensectomy and vitrectomy side effects were mostly changes in refractory error and retinal detachment.

Comparison of first and last Autoref reading of right and left eyes are shown in Table 3. There were insignificant difference between first and last Autoref readings in spherical error, cylinder error, and axis of right eyes (P = 0.068, P = 0.285, and P = 0.068) and left eyes (P = 0.109, P = 0.109, and P = 0.655) (Table 3).

Discussion

Cysteine β-synthase insufficiency is the most common cause of homocystinuria, and it manifests as elevated serum homocysteine levels and positive urine homocysteine tests. Fibroblasts can be definitively identified by enzyme deficiency[3]. The condition affects the skeletal, circulatory, ocular, and central neurological systems. These patients frequently experience thromboembolic events, progressive mental impairment, and skeletal disorders such as anomalies in the chest[3,15,16]. Six patients with HCU were reported in this hospital-based retrospective study. In this study, HCU patients' age ranged from 22 to 30 years with mean of 26.17 years. Age therapy commenced ranged from 3 to 11 years with mean of 8.33 years. In this research, associated diseases were mostly mental retardation (100%), epilepsy (66.7%), developmental delay (50.0%), scoliosis (33.3%), bronchiectasis (16.7%), thrombophilia (16.7%),

Table 2

Ophthalmic conditions and types of surgeries of patients (n = 6).

Parameters	Value
Ophthalmic conditions	
Ectopia lentis	6 (100%)
Eye ectropion	1 (16.7%)
Anterior uveitis	1 (16.7%)
Scleromalacia	1 (16.7%)
Surgeries	
Lensectomy and vitrectomy (ppl and ppv)	5 (83.3%)
Scleral fixation	1 (16.7%)
Grice green procedure	1 (16.7%)

Table 3

First and last Autoref reading of right and left eyes (n = 6).

Parameters	First Autoref reading	Last Autoref reading	Significance
Right eye			
Spherical error	−11.13 (−14.88 to −6.63)	9.25 (1.06–14.63)	0.068
Cylinder error	−1.63 (−2.75 to −0.69)	−1.75 (−1.75 to −1.31)	0.285
Axis	135.00 (54.50–172.75)	125.00 (43.75–167.25)	0.068
Left eye			
Spherical error	−11.88 (−15.00 to −6.69)	9.75 (9.75–9.75)	0.109
Cylinder error	−1.75 (−4.75 to −0.63)	−1.75 (−2.00 to −1.75)	0.109
Axis	88.00 (16.50–161.00)	152.00 (9.00–152.00)	0.655

metabolic diseases (16.7%) and DVT (16.7%). The patients were received the appropriate therapy for the associated morbidities. A comprehensive approach that addresses the metabolic deficiency and secondary consequences is usually necessary for the treatment of HCU with related morbidities. Neurological damage can be reduced with strict dietary management, including a low-methionine diet and supplements of cysteine and vitamins (such as pyridoxine, folate, and B12). Take part in individualized cognitive and behavioral therapy. To prevent interfering with metabolic therapies, use seizure-specific drugs carefully. Braces and routine physical treatment were used by scoliosis patients to maintain their posture and muscular strength. Antibiotics were used to treat respiratory infections in patients with bronchiectasis. Vitamins to promote enzymatic activity and betaine to lower homocysteine levels were administered to patients with metabolic disorders. In Saudi Arabia, the majority of HCU patients have a delayed diagnosis. This was shown in 2011 by Zaidi *et al*[17], who presented a case series of patients with HCU from Saudi Arabia and Sudan who were detected later than expected and so typically presented with comorbidities such as ectopia lentis, thrombosis, developmental delay, and skeletal deformity[17]. People with HCU who had an early neonatal screening (NBS) diagnosis are anticipated to grow and develop normally or almost normally. According to Gan-Schreier *et al.*[18], 14 patients with HCU detected by NBS in Qatar over the course of three years; all of them showed normal growth and development. This shows that NBS is a practical and successful treatment for homocystinuria. It avoids the skeletal, ocular, and developmental delays linked to HCU.

Patients in HCUs may experience significant quality-of-life compromise due to ocular issues. In this study, ocular complications were ectopia lentis (100%), eye ectropion (16.7%), anterior uveitis (16.7%), and scleromalacia (16.7%). High myopia, ectopia lentis, iridodonesis, cataracts, retinal detachment, microcystoid peripheral retinal degeneration, secondary pupillary block glaucoma, retinal detachment, optic atrophy, retinal artery occlusions, and band keratopathy were the most prominent eye conditions observed in HCU patient[2,19]. Ectopia lentis affects about 70% of patients with HCU till the age of 7, increasing to 95% by the fifth decade[20]. Patients as young as three years old have been reported to have lens displacement[21]. Lens instability, an elevated refractive index, iridodonesis, and globe enlargement are all associated with weak Zinn and sclera zonules, and they all contribute to progressive myopia in children. Approximately 45% of patients with HCUs have high myopia[5,12]. A lack of suture following lens removal can also lead to high myopia. According to earlier studies, pathological alterations in weak scleral

connective tissue are linked to high myopia, which was seen in nearly 45% of cases of homocystinuria[21]. According to Hsia *et al*, myopic tractional maculopathy is the only condition where a lamellar macular hole is linked to retinoschisis[22]. High myopia is related with a higher incidence of posterior vitreous adhesion and epiretinal proliferation linked to lamellar holes[23]. These conditions can potentially be caused by changes in scleral connective tissue and irregular scars. Non-normal collagen fibers in the corneal stroma might be associated with keratoconus. There is a chance that these anomalies will make the eye's connective tissue structures less resilient to intraocular pressure[21]. The significant movability of the lens in patients with HCU may result in anterior or posterior lens luxation, with or without angle-closure glaucoma[5]. In these series of glaucoma patients, all intraocular pressure levels were high following lens extraction without intraocular lens insertion, and aphakia is a risk factor for glaucoma perse (also known as aphakic glaucoma)[21]. Glaucoma leads to the progressive loss of peripheral vision, which may go unnoticed in the early stages. Damage to the optic nerve over time reduces central visual acuity, affecting tasks requiring fine focus, such as reading or recognizing faces. Patients may have difficulty distinguishing between objects with low contrast, further impacting functional vision in dim lighting or low-contrast environments. Glaucoma can cause increased sensitivity to light and difficulties with glare, compounding the visual impairments already present in HCU.

Clinical ocular manifestations in HCU patients are thought to be caused by biochemical anomalies, although the underlying mechanisms are not entirely clear. Given that the lens zonules contain high cysteine content, ocular disorders may be associated with a decreased cysteine level[3,5]. Increased tHcy concentrations alter the sulfhydryl groups on proteins and prevent them from cross-linking to form proteins like elastin[3]. The differential diagnosis of HCU from other disorders that have similar clinical, biochemical, or genetic characteristics as methylenetetrahydrofolate reductase and other hereditary abnormalities of homocysteine metabolism, as well as deficiencies and disorders of cobalamin metabolism (e.g. cobalamin C, D defects) must be assessed. Additionally, Marfan syndrome shared with HCU skeletal and visual characteristics including ectopia lentis and scoliosis. Meanwhile, Marfan syndrome does not, however, have thromboembolism or homocysteine biochemical abnormalities. Scoliosis, connective tissue abnormalities, and joint hypermobility are all possible symptoms of Ehlers-Danlos Syndrome. Nevertheless, Ehlers-Danlos Syndrome is not linked to hyperhomocysteinemia, ectopia lentis, or thromboembolism. Chronic kidney disease and drug-induced hyperhomocysteinemia, such as that brought on by methotrexate, can both result in acquired hyperhomocysteinemia[24]. Combining genetic testing, biochemical assays, and clinical evaluation is necessary for an accurate diagnosis. To differentiate HCU from remethylation abnormalities or diseases of cobalamin metabolism, plasma homocysteine, and methionine levels are essential[25]. While other markers (such as methylmalonic acid and vitamin levels) help to refine differential diagnosis, genetic tests validate specific mutations[24].

It is commonly known that early detection might stop HCU's ocular symptoms. Patients with HCU require supplements of vitamin B6, pyridoxine, along with a low-methionine diet[26]. To avoid recurring thromboembolic problems, several researchers advise taking multivitamin pills that contain folic acid, B6, and B12[27]. In this study, the types of surgery made for HCU patients were mostly lensectomy and vitrectomy (83.3%) then scleral fixation (16.7%), and Grice green procedure (16.7%). After treatment, there were insignificant differences between first and last Autoref readings in spherical error, cylinder error, and axis of right and left eyes. Ectopia lentis therapy is still debatable, though. When a patient has anterior lens dislocation, surgical surgery is advised, regardless of whether they also have secondary acute glaucoma. When a lens is displaced into the vitreous cavity, surgical options must be carefully considered because postoperative retinal detachment and vitreal prolapse have been documented[28]. Age is correlated with more zonular disruption in homocystinuria and hence greater lens mobility. Consequently, at older ages, total anterior lens displacement may be observed[29]. Pediatricians and anesthesiologists should be consulted before deciding whether to proceed with surgery because general anesthesia in these patients may increase the risk of thrombosis[30]. Lensectomy, which involves aspirating or extracting the crystalline lens, is the most often performed surgical surgery on HCU patients[31]. This can usually be completed without causing vitreous loss. Because the vitreous remains adherent to the crystalline lens in younger patients, vitreous loss and problems such retinal detachment may result with lens extraction. Retinal detachment as a result of vitreous loss is rare, although it can occur as a long-term postoperative consequence[32,33]. An iris-fixated intraocular lens (IOL) must be implanted when these patients' compliance with aphakic refractive corrections (such as glasses or contact lenses) is insufficient and there is a significant risk of amblyopia. Implantation of scleral-fixated IOL is advised by certain researchers. However, patients require long-term follow-up since there is a substantial future risk of suture breakdown and IOL dislocation[31]. Other research recommended fitting children with anterior lens displacement with foldable IOLs that are fixed to the iris. They demonstrated that there are no significant problems following this surgical treatment, and appropriate anatomical and functional results are obtained. Furthermore, transscleral suture fixation is not required in contrast to scleral-fixated IOL implantation surgery[34,35]. According to Miraftabi *et al*[36], the patient in question declined to use a high-myopic eyeglasses. Concerns were also raised over the proper usage of contact lenses and the adherence to long-term follow-up exams. Consequently, in order to lower the risk of amblyopia, they favored implanting an iris-fixated IOL and using spectacles to rectify any residual refractive error.

Limitations of this study were small sample size, one tertiary hospital-based study and retrospective nature of the study. Also, another limitation of the study was that enzyme activity and genetic results assay were not recorded.

Conclusions

This group of patients with late diagnosis from HCU was found to have many ocular abnormalities. When ectopia lentis is unintentionally discovered during an eye exam, the optometrist or ophthalmologist should add HCU to the differential diagnosis. Children should have dilated slit lamp examinations as part of all eye exams, and if ectopia lentis is found, the patient should be referred right away for a genetic evaluation.

Ethical approval

Ethical approval for this study (Approval # 2023-56) was provided by the Health Research Ethics Committee of King Abdulaziz University, Jeddah, Saudi Arabia on 16 August 2023.

Consent

Written informed consent was obtained from the patient for publication. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflicts of interest disclosure

None.

Sources of funding

None.

Author's contribution

Conceptualization: A.S.A., M.T.H., and E.Y.D.; methodology: A.S.A., M.T.H., and E.Y.D.; software: A.S.A.; validation: A.S.A., M.T.H., E.Y.D., E.A.A., and F.F.A.; formal analysis: A.Y.D. and M.T.H.; investigation: M.T.H. and E.Y.D.; resources: A.S.A., H.A.A., M.T.H., E.Y.D., E.A.A., and F.F.A.; data curation: E.Y.D., E.A.A., and F.F.A.; writing – original draft preparation: A.S.A., M.T.H., E.Y.D., E.A.A., and F.F.A.; writing – review and editing: M.T.H. and E.Y.D.; visualization: A.S.A., H.A.A., M.T.H., E.Y.D., E.A.A., and F.F.A.; supervision: M.T.H. and E.Y.D.; project administration: A.S.A. All authors contributed toward data analysis, drafting, and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Guarantor

None.

Research registration unique identifying number (UIN)

ClinicalTrials.gov ID NCT06545305.

Provenance and peer review

Not invited.

Data availability statement

Data of original research with corresponding author and will be provided when required.

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