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PATIENTS WITH HOMOCYSTINURIA PRESENTING TO NEUROLOGY CLINIC IN CHILDREN WELFARE TEACHING HOSPITAL MEDICAL CITY COMPLEX

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ABSTRACT

Background: Metabolic screening for children with intellectual impairment, ectopia lentis, global developmental delay, and/or vascular events is recommended for early detection of homocystinuria. Despite the expansion of neonatal metabolic screening in many countries, it remains underutilized in others, emphasizing the need for heightened clinical suspicion. **Aim:** To analyze the clinical and biochemical profiles of patients diagnosed with homocystinuria in a pediatric neurology clinic. **Methods:** A single-center investigation was undertaken at the Paediatric Neurology Department. Plasma samples from 600 individuals with unexplained neurological abnormalities, developmental delay, visual impairment, stroke-like symptoms, behavioral problems, and seizures were examined. Mass spectrophotometry and HPLC proved homocystinuria in 33 cases. Classical (elevated methionine) and non-classical (normal/low methionine) subtypes were identified, with the classical group further classified as B6 responsive or not. **Results:** Of 600 patients, 33 (5.5%) had homocystinuria: 29 classical (20.6% B6 responsive, 79.4% non-B6 responsive) and 4 non-classical. Classical patients had global developmental delay (48.3%), hemiplegia (24.1%), ophthalmological referral (20.7%), or seizures (6.9%), whereas non-classical cases had global delay (75%) and seizures (25%). Non-classical individuals had blond eyes but no myopia or ectopia lentis, while classical cases had 72% ocular involvement. Classical patients showed vascular ischaemia (34.5%) and atrophy (58.5%) on brain MRI, whereas all non-classical cases showed microangiopathic alterations and atrophy. **Conclusion:** In the absence of newborn screening, homocystinuria remains a significant diagnosis in neurologically disordered patients, often delayed. Clinical awareness and accurate biochemical testing are crucial for timely diagnosis and management.

KEYWORDS: Homocystinuria, neurology clinic in children welfare teaching hospital.

INTRODUCTION

Inborn errors of metabolism (IEMs) are a diverse group of rare genetic disorders caused by enzyme or transport protein defects that disrupt metabolic pathways.[1] These disruptions result in toxic substrate accumulation, alternative pathway metabolites, or deficiencies in energy production, often affecting the central nervous system (CNS) and causing neurological disease.[2, 3] With over 1,000 inherited disorders classified as IEMs, their presentation spans a spectrum of phenotypes influenced by environmental, epigenetic, and genetic factors, complicating genotype-phenotype correlation and disease prediction.[4] The overall incidence of IEMs is estimated at 1 in 800 live births, varying across populations due to racial, ethnic, and screening program differences.[5] Expanded newborn screening (NBS) using tandem mass spectrometry has become a public health priority in many countries, improving early detection and outcomes.[1] However, in Iraq, the NBS program implemented in 2010 excludes screening for homocystinuria (HCU), with diagnostic tests limited to a few private laboratories. High rates of consanguineous marriages in Iraq further elevate the prevalence of autosomal recessive IEMs. Promising local data on IEM incidence and presentation highlight opportunities for improved management strategies. IEMs are categorized as: metabolite accumulation and intoxication disorders (e.g., aminoacidopathies, organic acidemias, urea cycle defects), energy metabolism impairments (e.g., mitochondrial disorders, fatty acid oxidation defects), and complex molecule metabolism disruptions (e.g., lysosomal and peroxisomal disorders).[6] Aminoacidopathies, such as homocystinuria, are diagnosed via plasma amino acid assays and often present with early encephalopathy.[6] Homocystinuria, an autosomal recessive disorder caused by mutations in the

cystathionine β-synthase (CBS) gene on chromosome 21q22.3, affects methionine metabolism and manifests variably across systems, including ocular, skeletal, vascular, and CNS involvement.[7] Clinical signs often appear after three years, with ectopia lentis being a hallmark feature.[8] Other manifestations include intellectual disability, seizures, and thromboembolic events. Brain imaging typically shows vascular abnormalities such as microangiopathy and infarcts.[9, 10] Homocystinuria is classified as classical (elevated methionine) or non-classical (normal/low methionine). Classical cases may be B6-responsive or non-responsive, influencing management strategies.[8] Non-classical forms, caused by defects in methylcobalamin formation or methylenetetrahydrofolate reductase deficiency, present with varied severity and require specialized treatment, including hydroxycobalamin and betaine supplementation.[11,12] In the absence of comprehensive NBS programs, early diagnosis of HCU depends on clinical awareness and biochemical testing, underscoring the need for improved diagnostic and management practices in Iraq. The study aimed to highlight homocystinuria patients' key clinical aspects. To explore homocystinuria kinds and features. To explore prevalent homocystinuria consequences.

METHOD

This single-center study was conducted at the Pediatric Neurology Department and Clinic at the Welfare Teaching Hospital, Medical City, Baghdad, from October 1, 2018, to October 1, 2019. A total of 600 patients suspected of inborn errors of metabolism (IEM) were referred for fluorescent high-performance liquid chromatography (HPLC) analysis. Patients were selected based on a high index of suspicion warranting confirmatory amino acid analysis and/or suspected homocystinuria (HCU) indicated by tandem mass spectrometry (MS/MS). Among these, 39 patients were initially diagnosed with HCU, but 6 were excluded due to loss of follow-up, leaving 33 patients for the final analysis.

Inclusion Criteria: Patients aged 1 month to 18 years presenting with unexplained neurological deficits, developmental delay, visual impairment, seizures, vascular events, positive family history, behavioral abnormalities, skeletal deformities, or unusual body/urine odor. A significant increase in blood homocysteine levels on more than one measurement was required.

Exclusion Criteria: Patients younger than 1 month or older than 18 years and those lost to follow-up.

Clinical Evaluation: Patients underwent thorough clinical and neurological evaluations. Ophthalmological assessments were conducted to identify myopia, ectopia lentis, and other ocular features. General examinations focused on eye, skin, and hair color, skeletal deformities, stature, and Marfanoid habitus. Behavioral abnormalities were assessed collaboratively with pediatric psychiatrists. Consanguinity status was also documented.

Laboratory Investigations: Basic metabolic tests included blood glucose, electrolytes, liver function tests, arterial blood gases, ammonia, and lactate as needed. Brain MRI, MRA, and MRV findings were reviewed for atrophy, microangiopathy, sinus thrombosis, and ischemic strokes. Specific tests included fasting blood homocysteine (normal: 4-40 µmol/L) and methionine levels (normal: 4-65 µmol/L). Methionine levels differentiated classical HCU (elevated) from non-classical HCU (normal or low). B6 responsiveness was tested by administering high doses of vitamin B6 (250 mg twice daily) and monitoring homocysteine levels.

Statistical Analysis: Data were analyzed using SPSS version 21.0. Results were presented as mean ± SD for quantitative variables and frequency and percentage for qualitative variables.

RESULTS

A total of 33 cases of homocystinuria were studied, comprising 29 (87.8%) classical and 4 (12.2%) non-classical cases.

Vitamin B6 Responsiveness: In the classical group, 6 cases (20.6%) were responsive to vitamin B6, while 23 cases (79.4%) were non-responsive.

Demographics: The mean age of classical HCU cases was 9.65 ± 4.51 years (range: 3–18 years), with a male-to-female ratio of 3:1 (23 males, 7 females). In the non-classical group, the mean age was 6.75 ± 2.98 years (range: 3–10 years), with 1 male (25%) and 3 females (75%). (Tables 1 and 2).

Delay in Diagnosis: In the classical group, the mean age at diagnosis was 4.77 ± 3.81 years (range: 1 month–16 years), with an average diagnostic delay of 4.88 ± 4.36 years (range: 0–15 years) from symptom onset to diagnosis. In the non-classical group, the mean age at diagnosis was 3.00 ± 0.82 years (range: 2–4 years), with an average diagnostic delay of 3.75 ± 2.5 years (range: 1–7 years). (Tables 1 and 2).

Biochemical Findings: The mean plasma homocysteine level in the classical group was 268.76 ± 137.52 µmol/L (range: 34.2–667.0), with a median of 283.0 µmol/L. In the non-classical group, the mean homocysteine level was 284.5 ± 150.10 µmol/L (range: 110–455), with a median of 286.5 µmol/L. Methionine levels in the classical group averaged 528.93 ± 398.02 µmol/L (range: 101–1483), with a median of 410 µmol/L. In the non-classical group, the mean methionine level was 23.0 ± 2.94 µmol/L (range: 20–70), with a median of 22.5 µmol/L. (Tables 1 and 2).

Table1: Classical HCU group age, delay in diagnosis and levels of homocystine and methionine.

	Age	Age of diagnosis	year since manifestations	homocysteine level	methionine level
Mean	9.66	4.77	4.88	268.76	528.93
SD	4.51	3.81	4.36	137.52	398.03
Min	3.00	0.16	0.00	34.20	101.00
Max	18.00	16.00	15.00	667.00	1483.00
Median	9.00	4.00	3.50	283.00	410.00

Table 2: Non classical HCU group age, delay in diagnosis and levels of homocystine and methionine.

	Age	age of diagnosis	year since manifestations	homocystein level	methionin level
Mean	6.75	3.00	3.75	284.50	23.00
SD	2.99	0.82	2.50	150.10	2.94
Min	3.00	2.00	1.00	110.00	20.00
Max	10.00	4.00	7.00	455.00	27.00
Median	7.00	3.00	3.50	286.50	22.50

Consanguinity distribution: was 16 (55.1%) first cousin, 2 (10.3%) second cousin, 4 (13.8%) far related and 6 (20.8%) unrelated in the classical group; while it was all 4 (100%) cases first cousin in the non-classical group. Family history of HCU for our study cases; was 21 (72.4%) positive and 8 (37.6%) negative in the classical group; while it was 2 (50%) positive and 2 (50%) negative in the non-classical group.

Presentation history in the classical group was 14 (48.3%) cases presented with global developmental delay, 7 (24.1%) cases presented with hemiplegia, 6 (20.7%) cases were referred from the ophthalmologist as suspected cases of HCU, and 2 (6.9%) cases presented with seizure. While the non-classical group was 3 (75%) cases presented with global developmental delay and one (25%) case presented with seizure. As shown in table 3.

Table 3: Presenting features leading to diagnosis of HCU.

Presentation	Classical 29 cases	Non classical 4 cases
Referred from the ophthalmologist	6 (20.7%)	
Global developmental delay	14 (48.3%)	3 (75%)
Epilepsy	2 (6.9%)	1 (25%)
Hemiplegia	7 (24.1%)	

Skeletal involvement; in the classical group was 9 (31.0%) had short stature, 5 (17.2%) marfinoid with tall stature, 3 (10.3%) marfinoid with short stature and joint deformity, one (3.5%) with short stature and skeletal deformity and 9 (31.0%) cases with no skeletal involvement. In non-classical group one (25%) had facial dysmorphism and 3 (75%) cases with no skeletal involvement. So 100% of the no classical group had no skeletal involvement. As shown in table 4.

Table 4: Skeletal involvement in classical and non-classical HCU.

Features	Classical 29 cases	Non classical 4 cases
short stature	9 (31.0%)	
Marfinoid with tall stature	5 (17.2%)	
marfinoid and short stature with skeletal deformity	3 (10.3%)	
short stature and skeletal deformity	1 (3.5%)	
no involvement	9 (31.0%)	4 (100%)

Ocular involvement; in the classical group there were 21 (72%) cases had ocular manifestations including; 10 (34.5%) with myopia, 6 (20.7%) had myopia and surgery for ectopia lentis, 2 (6.9%) with myopia and blond eyes, 2 (6.9%) had blond eyes, one (3.5%) with squint and ectopia lentis and 8 (37.5%) with no involvement. In the non-classical group had 2 (50%) had blond eyes and 2 (50%) with no ocular features. No one in the non-classical group had myopia or ectopia lentis. Familial fair hair, skin and blond eyes were not considered. As shown in table 5.

Table 5: Ocular features in classical and non-classical HCU.

Ocular feature	Classical	Non classical
Myopia	10 (34.5%)	
Myopia, blond	2 (6.9%)	
Ectopia; **Operated**	7 (24.2%) 6 (20.7%)	

Not operated	1 (3.5%)	
Blond	2 (6.9%)	2 (50%)
No involvement	8 (37.5%)	2 (50%)

Behavioral status; in the classical group there were 19 (65.5%) cases having intellectual impairment, 3 (10.3%) cases had abnormal behavior, 3 (10.3%) cases had frank ADHD and 4 (13.9%) with no significant behavioral or intellectual manifestations. Non-classical group were all 4 (100%) with intellectual impairment. As shown in table 6.

Table 6: Behavioral status in classical and non-classical HCU.

Behavioral status	Classical 29 cases	Non classical 4 cases
Abnormal behavior	3 (10.3%)	
ADHD features	3 (10.3%)	
intellectual impairment	19 (65.5%)	4 (100%)
No involvement	4 (13.9%)	

Dermatological involvement; in the classical group there were 11 (37.9%) cases with fair hair and skin which was unusual in comparison to other family member's complexion, one (3.5%) case with fair hair and skin and hair loss, one (3.5%) case with fair hair and skin and nail destruction and 16 (55.1%) cases without involvement. Non-classical group there were 2 (50%) with fair hair and skin and 2 (50%) without coetaneous features.

Epilepsy; in the classical group 6 (20.7%) cases had epilepsy and 23 (79.3%) cases had no epilepsy. In the non-classical group one (25%) had epilepsy and 3 (75%) didn't have epilepsy.

Other involvements; in the classical group; 4 cases had spasticity, one case had ataxia and rigidity, one case had neonatal jaundice and anemia, one case complained from self-mutilation, one case had ataxia, rigidity, chorea and dystonia, two cases had dystonia and congenital heart disease (CHD), one case developed portal vein thrombosis, one case had disabling treatment resistant hemidystonia, one case had chronic headache and spasticity and one case had spasticity and cerebral venous sinus thrombosis. In non-classical group; one case had complex movement disorder and one case had severed spasticity. As shown in table 7.

Table 7: Other involvements in classical and non-classical HCU.

Classical	Non classical
4 cases had spasticity	1 case complex movement disorder
1case had ataxia rigidity	1 case spasticity
1with neonatal jaundice and anemia	
1case self-mutilation	
1case ataxia, rigidity, chorea, dystonia	
2 dystonia and CHD	
1case portal vein thrombosis	
1case hemidystonia	
1case chronic headache and spasticity	
1case spasticity and sinus thrombosis	

Brain MRI findings; in the classical group there were 10 (34.5%) cases with thromboembolic findings, 17 (58.5%) cases with atrophy, one (3.5%) case was fair and one (3.5%) case was not performed on. In the non-classical group; 2 (50%) cases had microangiopathic changes and brain atrophy, one (25%) case had microangiopathic changes with severe brain atrophy and one (25%) case had microangiopathic changes and moderate brain atrophy. As shown in table 8.

Table 8: Brain MRI findings in classical and non-classical HCU.

	Classical	Non classical
brain MRI findings	Atrophy 17 (58.5%)	Microangiopathic changes and severe atrophy 1 (25%)
	thromboembolic10 (34.5%)	Microangiopathic changes and moderate atrophy 1 (25%)
	Fair 1 (3.5%)	Microangiopathic changes and mild atrophy 2 (50%)
	Not done 1 (3.5%)	

DISCUSSION

Homocystinuria (HCU) is a rare autosomal recessive disorder with protean features, variable age of onset, and multisystem involvement. In this study, 33 HCU cases were analyzed, with 29 (87.8%) being classical and 4 (12.2%) non-classical, classified based on methionine levels. Vitamin B6 responsiveness was noted in 20.6% of classical cases, consistent with findings by Fatima S et al.[13] that B6 responsiveness varies across populations and phenotypes. This study reported a lower B6 responsiveness compared to Madhava M[14], possibly due to differences in sample size, genetic factors, or milder symptoms in B6-responsive patients. Males predominated in the classical group (79%, 3:1 ratio), a pattern also observed by Al-Dewik et al.[15] This gender disparity lacks a clear explanation, given the autosomal recessive inheritance. The delay in diagnosis—mean of 4.77 years in the classical group—highlights the need for better diagnostic protocols in regions lacking newborn screening. Classical HCU cases presented primarily with global developmental delay (48.3%), hemiplegia (24.1%), and ocular abnormalities (20.7%), findings consistent with previous studies.[13,16,17] Global developmental delay was the leading feature in non-classical HCU (75%), similar to findings by Manoli I et al.[11] Non-classical HCU was differentiated from MTHFR or methylcobalamin cofactor deficiencies by genetic studies, with one case showing methylmalonic acidemia. Consanguinity was prominent, with 79.2% of classical cases and 100% of non-classical cases born to consanguineous parents, aligning with the high prevalence of consanguinity in Iraq. Similar findings were reported by Al-Dewik et al.[15] and Soraia and Giovana et al.[16] Family history of similar features was observed in 72.4% of classical cases and 50% of non-classical cases. Ocular involvement was present in 62.5% of classical cases, including myopia, ectopia lentis, and blond eyes, consistent with studies by Mulvihill et al.[18] and Taylor and Burke et al.[19] In non-classical HCU, no cases of ectopia lentis or myopia were observed, agreeing with Georg et al.[20] Ectopia lentis is specific to classical HCU and typically occurs by age eight, particularly in B6 non-responsive patients. Seizures were the presenting feature in 6.9% of classical cases and 25% of non-classical cases, with epilepsy present in 20.7% of classical cases overall. This aligns with findings by Al-Dewik et al.[15] and Polani et al.[16] Seizures are associated with cerebral thrombi and electroencephalographic abnormalities, as noted by Hidalgo Mazzei D et al.[21] Skeletal abnormalities, including marfanoid habitus and short stature, were observed in 31% of classical cases, consistent with Sacharow et al.[22] and Karaca M, et al.[23] No skeletal involvement was noted in non-classical cases. Behavioral abnormalities were present in 65.5% of classical cases and all non-classical cases, including intellectual impairment, ADHD, and psychiatric manifestations. This is consistent with studies by Al-Dewik et al.[15] and Hidalgo Mazzei D et al.[21] Brain MRI findings showed thromboembolic events and atrophy in 93% of classical cases and microangiopathic changes in all non-classical cases. These findings corroborate studies by Karimzadeh et al.[24] and Sachdeva et al.[25], emphasizing the importance of neuroimaging in evaluating HCU patients. Routine MRI surveillance, however, is not recommended without neurological symptoms.[26] This study highlights the variability in HCU presentation, emphasizing the importance of clinical awareness and early diagnosis to reduce morbidity and improve outcomes. Further genetic and epidemiological research is needed to better understand regional and phenotypic variations in HCU.

CONCLUSION

Classical HCU is more common than non-classical HCU. Classical HCU affects a comparatively greater number of males than girls. Ectopia lentis and marfinoid habitus are distinguishing characteristics of classical HCU, absent in non-classical HCU. The majority of individuals with all forms of HCU have alterations in brain MRI.

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