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Comprehensive Analysis of Persistent Isolated Hypermethioninemia: A Single Centre Study in Korea Over Two Decades

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KEYWORDS Aminoacid Metabolism. Genetic Testing. Hypermethioninemia. Neonatal Screening. Phenotype

ABSTRACT Persistent isolated hypermethioninemia (PIH) is a metabolic condition primarily caused by methionine adenosyltransferase I/III (MATI/III) deficiency due to a variant in the MAT1A gene. This retrospective study aimed to evaluate the prevalence, genetic spectrum, and clinical outcomes of PIH identified through newborn screening (NBS) at a single centre in Korea. A total of 46 patients referred for hypermethioninemia between March 1999 and July 2023 were reviewed. Among 46 patients, 30 were diagnosed with PIH, 8 with homocystinuria, and 8 with transient hypermethioninemia. PIH patients showed a significant decrease in methionine levels over time. Genetic analysis revealed *MAT1A* variants, including the novel variant R84K, in all 30 PIH patients. The study underscores the importance of NBS in early detection and suggests that PIH typically presents a favourable prognosis, emphasising the need for expanded screening and tailored management strategies.

INTRODUCTION

Methionine (Met) is a essential amino acid that serves as a marker in newborn screening (NBS) for detecting various inborn errors of metabolism (Huemer et al. 2015). Elevated levels of methionine can be observed in certain conditions such as liver disease or premature infants, but it primarily indicates specific metabolic disorders. These disorders include cystathionine-â-synthase (CBS) deficiency (OMIM # 236200), glycine N-methyltransferase (GNMT) deficiency (OMIM # 606664), and methionine adenosyltransferase I/III (MAT I/III) deficiency (OMIM # 250850) or Mudd's disease, named after the respected expert on hypermethioninemia, S. Harvey Mudd (Hübner et al. 2022).

MAT I/III deficiency is the most common cause of hypermethioninemia in patients undergoing NBS. This metabolic disorder can be inherited in either autosomal dominant (AD) or recessive (AR) patterns due to variants in the *MAT1A* gene, leading to persistent isolated hypermethioninemia (PIH) (Zhao et al. 2022). The clinical manifestations of MAT I/III deficiency vary based on the mode of inheritance but generally have a more favourable prognosis than conditions such as homocystinuria (Huemer et al. 2015; Sen et al. 2019; Zhang et al. 2020). However, recent studies suggest that the clinical outcomes of MAT I/III deficiency are more heterogeneous than previously recognised, with neurological complications reported in some patients with the autosomal recessive form (Ma et al. 2024). As newborn screening programs continue to expand globally, the number of infants referred for elevated methionine is increasing, necessitating a clearer understanding of the long-term prognosis of PIH.

In this retrospective study, the researchers report an analysis of 46 cases of hypermethioninemia detected through NBS, employing comprehensive differentiation techniques including plasma amino acid analysis, plasma homocysteine measurement, and genetic analysis (Kim et al. 2016).

By delving into the etiology and clinical presentation of hypermethioninemia, this study aimed to shed light on PIH confirmed through genetic analysis at a single centre over 20 years. The identification and characterisation of these cases have significant implications for early diagnosis, treatment, and management of hypermethioninemia-related conditions. This study is unique because of its extensive analysis over a 20-year period at a single centre in Korea, representing one of the most comprehensive investigations of persistent isolated hypermethioninemia (PIH) in the region. This study also pro-

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vides novel insights by identifying a previously unreported *MAT1A* gene variant, expanding the known genetic spectrum of PIH. Furthermore, it highlights the varying inheritance patterns and their clinical implications, offering new perspectives on genetic counseling and management of patients with PIH.

The insights gained from this long-term investigation will contribute to a deeper understanding of this disorder and pave the way for improved clinical strategies and patient outcomes.

Objectives

The objectives of this study were to:

1. Analyse the prevalence and etiological spectrum of hypermethioninemia identified through NBS at a single tertiary centre in Korea over a 20-year period
2. Characterise the genetic variants and inheritance patterns of the MAT1A gene in patients with PIH
3. Evaluate the long-term clinical outcomes of PIH to provide evidence for the management of infants with elevated methionine on NBS.

MATERIAL AND METHODS

Study Population

This study involved a cohort of 46 patients (26 girls and 20 boys) with hypermethioninemia who were referred to the pediatrics department of Soonchunhyang University Seoul Hospital for NBS between March 1999 and July 2023. Patients were identified based on elevated methionine levels detected during tandem mass spectrometry (MS/MS)-based NBS. Over the 24-year study period, physicians, neonatologists, and geneticists caring for these newborns followed homogeneous strategies for diagnosis and management. These strategies included standardised protocols for newborn screening, confirmatory testing, genetic analysis, and management of hypermethioninemia to ensure consistent care across all cases.

Diagnosis Confirmation

The diagnosis of hypermethioninemia was confirmed through a comprehensive analysis of plasma amino acids using liquid chromatography (LC)-MS/MS with MassChrom®. In this study, hypermethioninemia was initially identified when plasma methionine levels exceeded 47 umol/L during newborn screening. Total homocysteine (tHcy) was subsequently measured as a second-tier test, with concentrations above 14 umol/L used to support differentiation between MAT I/III deficiency, CBS deficiency, and other causes. Thus, plasma methionine served as the primary diagnostic marker for hypermethioninemia, whereas elevated tHcy provided additional information regarding the underlying etiology (Sen et al. 2019).

Genetic Analysis

For patients with PIH, a genetic analysis of the *MAT1A* gene was conducted to identify the specific variants responsible for the condition. Genomic DNA was extracted from blood samples collected from the patients, and Sanger sequencing was performed to analyse the *MAT1A* gene using Sequencher software (version 5.4.6, build 46289; Gene Codes Corporation, Registration number 7006004). The PCR product required for sequencing was amplified using a C1000 Thermal Cycler from Bio-Rad, and sequencing was carried out on an AB 3500 Genetic Analyser (Thermo Fisher). This analysis was focused on identifying variants at specific sites associated with MAT I/III deficiency in the *MAT1A* gene (Li et al. 2023; Tong et al. 2023).

Data Collection and Analysis

Clinical and laboratory data, including patient demographics, plasma amino acid, and homocysteine levels, as well as genetic findings, were collected and recorded. The data were analysed to identify the prevalence of hypermethioninemia, differentiate between PIH and other related conditions such as homocystinuria, and determine the distribution of *MAT1A* gene variants among patients with PIH. Clinical phenotypes were evaluated through review of medical records, developmental history, and neurological examinations conducted during outpatient follow-up. When available, standardised cognitive or IQ testing results were also incorporated into the assessment. Patients without neurologi-

cal symptoms or developmental delay in these evaluations were considered clinically normal.

Ethical Considerations

This study was conducted in accordance with the ethical guidelines and regulations of the Institutional Review Board (IRB) of Soonchunhyang University Seoul Hospital (2022-06-013). Informed consent was obtained from the patients' parents or legal guardians before including their data in the study. Patient confidentiality and data protection were ensured throughout the study.

Statistical Analysis

Descriptive statistics were used to summarise the demographic and clinical characteristics of the study population. Categorical data were reported as frequencies and percentages, while continuous data were expressed as means with standard deviations or as medians with ranges, as appropriate. All statistical analyses were conducted using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Significant associations or correlations between variables were evaluated using appropriate statistical tests, and *p*-values of less than 0.05 were considered statistically significant.

RESULTS

Differential Diagnosis of Hypermethioninemia on NBS

The prevalence of PIH was examined among 46 patients referred to the paediatrics department for hypermethioninemia. Table 1 shows the laboratory and clinical findings of the referred hypermethioninemia patients -> of patients referred for hypermethioninemia. Several patients were diagnosed later because, although initially identified through NBS, they did not return to the hospital for confirmatory evaluation until a considerable time had passed. Differential diagnoses were made by identifying plasma amino acid and plasma homocysteine levels. Among these infants, 30 were diagnosed with PIH, 8 with isolated homocystinuria, and the remaining 8 patients exhibited transient hypermethioninemia (Fig. 1). Patients with PIH displayed an average initial plasma methionine level of 248.3 ìmol/L (range, 56.3-981.9, with reference ranges varying but all being 50 µmol/L or less) (Table 1). Out of ->the 30 patients who underwent regular plasma amino acid measurements, the majority (28 out of 30) showed a substantial decrease in plasma methionine levels to an average of 132.8 µmol/L (range, 56.3-981.9) during follow-up. The remaining two patients were referred to other healthcare centres after their diagnosis had been confirmed due to geographical reasons.

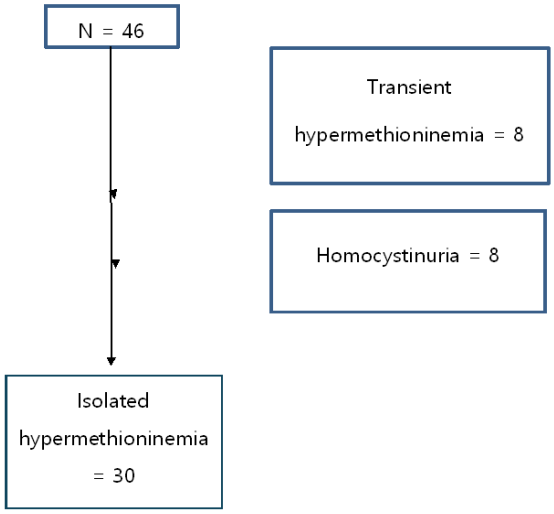

Fig. 1. Classification of 46 patients with elevated methionine levels on NBS

Table 1: Initial laboratory and clinical data of patients with hypermethioninemia

Sample number	*Gender (F/M)*	*Current age (years)*	*Gestational age (weeks)*	*Birth weight (kg)*	*Age at diagnosis (days)*	*Initial screening*		*Gene*	*Mutation site (cDNA/protein)*	*Inheritance*
						Methionine (μmol/L)	*Homocysteine (μmol/L)*			
S1	M	24	41+0	4.13	55	981.93	4.51	*MAT1A*	c.790G>A[p.R264H]	AD
S2	F	19	40+6	2.9	9	212	8.14	*MAT1A*	c.790G>A[p.R264H]	AD
S3	F	23	40+0	3.6	36	436.6	<1	*MAT1A*	c.790G>A[p.R264H]	AD
S4	F	16	40+0	3.2	36	165	<1	*MAT1A*	c.1161G>A[p.W387X] /c.895C>T[p.R299C]	AR
S5	M	15	40+0	3.7	36	225.9	<1	*MAT1A*	c.895C>T[p.R299C] /c.1067G>A[p.R356Q]	AR
S6	F	15	39+0	3.14	47	119.68	<1	*MAT1A*	c.776C>T[p.A259V]	AD
S7	F	14	40+0	3.24	28	250	<1	*MAT1A*	c.790G>A[p.R264H]	AD
S8	F	15	40+0	3.8	19	255	<1	*MAT1A*	c.790G>A[p.R264H]	AD
*S9	F	12	40+0	2.88	53	1108	26.5	*MAT1A*	c.895C>T[p.R299C] /c.1067G>C[p.R356P]	AR
S10	F	11	32+0	1.67	61	557	5.58	*MAT1A*	c.790G>A[p.R264H]	AD
S11	M	11	39+0	3.12	20	163.5	8.85	*MAT1A*	c.790G>A[p.R264H]	AD
S12	F	11	39+0	3.35	56	408.8	<1	*MAT1A*	c.790G>A[p.R264H]	AD
S13	F	7	39+0	3.2	37	280.5	<1	*MAT1A*	c.790G>A[p.R264H]	AD
S14	F	6	37+6	2.08	53	494	<1	*MAT1A*	c.790G>A[p.R264H]	AD
S15	F	5	38+0	3.1	29	68.6	N/A	*MAT1A*	c.790G>A[p.R264H]	AD
S16	F	5	39+6	3.5	53	88.4	<1	*MAT1A*	c.746G>A[p.R249Q]	AD
S17	M	5	36+6	3.24	38	95	<1	*MAT1A*	c.895C>T [p.R299C]	AD
S18	F	5	41+1	3.7	83	290	11.5	*MAT1A*	c.529C>T[p.R177W]/c.241C>T[p.R81W]	AR
S19	F	5	40+2	3.46	91	315.6	<1	*MAT1A*	c.790G>A[p.R264H]	AD
S20	F	3	37+5	2.16	15	78.72	<1	*MAT1A*	c.746G>A [p.R249Q]	AD
S21	F	4	39+2	3.64	31	85.46	<1	*MAT1A*	c.746G>A[p.R249Q]	AD
S22	F	3	39+2	3.23	30	110.6	<1	*MAT1A*	c.350T>C[p.I117T]/(-)	AR
S23	F	4	38+4	3.2	24	76	<1	*MAT1A*	c.1132G>A[p.G378S]/(-)	AR
S24	M	4	39+6	3.41	14	58.06	<1	*MAT1A*	c.529C>T[p.R177W]/(-)	AR
S25	F	5	39+3	2.8	20	81.45	<1	*MAT1A*	c.529C>T[p.R177W]/(-)	AR
S26	F	2	38+3	2.76	68	170.83	<1	*MAT1A*	c.395C>T[p.A132V]	AD
S27	M	0.2	37+3	3.09	37	56.27	1.3	*MAT1A*	c.745C>G[p.R249G]	AD
S28	F	2	38+5	3.18	18	76.976	<1	*MAT1A*	c.745C>G[p.R249G]	AD
S29	M	2	37+0	2.8 (twin)	43	70	<1	*MAT1A*	c.251G>A[p.R84K]/(-)	AR
S30	M	2	37+0	2.6 (twin)	74	70	N/A	*MAT1A*	c.251G>A[p.R84K]/(-)	AR
S31	M	21	39+2	3.39	59	141.47	7.56	NA	NA	NA
S32	M	21	N/A	N/A	475	175	5.58	NA	NA	NA
S33	M	18	40+0	3	13	81.06	10.82	NA	NA	NA
S34	M	17	40+0	3.28	189	155	8.04	NA	NA	NA
S35	F	17	40+0	3.6	18	132.63	5.1	NA	NA	NA
S36	M	15	39+0	3.7	72	114.95	N/A	NA	NA	NA
S37	M	14	38+0	3.2	63	359	7.92	NA	NA	NA
S38	M	8	38+1	3.6	32	64.3	8	NA	NA	NA
S39	M	4	38+1	3.31	37	792.1	147	*CBS*	c.545_546delGC[p.Ala183Glyfs*7]/c.694C>G[p.His232Asp]	AR
S40	F	17	38+6	3.02	72	817	101	*CBS*	c.634_634+8del9[?]/(-)	AR

Table 1: Contd...

Sample number	Gender (F/M)	Current age (years)	Gestational age (weeks)	Birth weight (kg)	Age at diagnosis (days)	Initial screening		Gene	Mutation site (cDNA/protein)	Inheritance
						Methionine (µmol/L)	Homocysteine (µmol/L)			
S41	M	18	N/A	N/A	8 years	993	N/A	*CBS*	c.407T>C[p.L136P]/ (-)	AR
S42	M	29	N/A	N/A	5 years	439.7	57.4	*CBS*	c.700_702delGAC[p.del234D]/c.770C>T[p.T257M]	AR
S43	M	21	36+0	2.4	52	1865.6	173.2	*CBS*	c.700_702delGAC[p.del234D]/c.770C>T[p.T257M]	AR
S44	F	22	39+0	N/A	94	1239	N/A	*CBS*	c.461T>A[p.L154Q] / (-)	AR
S45	M	3	39+1	2.97	9	256.7	136.2	*CBS*	c.1039G>A[p.Gly347Ser] / (-)	AR
S46	M	12	41+0	3.45	18	825	306.3	*CBS*	c.796A>G[p.R266G]/c.407T>C[p.L136P]	AR

Abbreviations: N/A, not available; MAT1A, methionine adenosyltransferase 1; CBS, cystathionine beta-synthase
[a]S9: this patient have mild intellectual disability (IQ 66) and was diagnosed

Table 2: Initial laboratory and genetic findings in patients with homocystinuria

S.No	Gender (F/M)	Age at diagnosis (days)	NBS results: methionine (ìmol/L)	Confirmatory plasma results		Gene	Mutation site
				Methionine (µmol/L)	Homocysteine (µmol/L)		
1	M	37	315	792.1	147	*CBS*	c.545_546delGC[p.Ala183Glyfs*7]/c.694C>G[p.His232Asp]
2	F	72	384	817	101	*CBS*	c.634_634+8del9[?]/(-)
3	M	8 yrs	N/A	993	N/A	*CBS*	c.407T>C[p.L136P]/ (-)
4	M	5 yrs	N/A	439.7	57.4	*CBS*	c.700_702delGAC[p.del234D]/c.770C>T[p.T257M]
5	M	52	265.3	1865.6	173.2	*CBS*	c.700_702delGAC[p.del234D]/c.770C>T[p.T257M]
6	F	94	801.6	1239	N/A	*CBS*	c.461T>A[p.L154Q] / (-)
7	M	9	103.6	256.7	136.2	*CBS*	c.1039G>A[p.Gly347Ser] / (-)
8	M	18	569	825	306.3	*CBS*	c.796A>G[p.R266G]/c.407T>C[p.L136P]

Abbreviations: N/A, not available; CBS, cystathionine beta-synthase

Patients with homocystinuria exhibited an average methionine level of 406.4 ìmol/L in NBS, along with a confirmatory plasma methionine level of 903.5 µmol/L (range, 256.7-1865.6). Their plasma homocysteine level was 135.5 µmol/L (range, 57.4-306.3) (Table 4). Genetic analysis identified *CBS* gene variants in all 8 patients (Table 2). In contrast, patients with transient hypermethioninemia showed a mean plasma methionine level of 152.6 µmol/L (range: 91.2-280) (Tables 3 and 4).

Variant Analysis of the *MAT1A* Gene in Persistent Isolated Hypermethioninemia

MAT1A gene variants were detected in patients with PIH. The genetic analysis revealed *MAT1A* variants in all 30 patients, with specific variants at c.790G>A[p.R264H], c.1161G> A[p.W387X], c.895C>T[p.R299C], c.1067G>A[p.R356Q], c.776C>T[p.A259V], c.529C>T[p.R177W], c.241C>T[p.R81W], c.350T>C[p,I117T], c.1132G>A [p.G378S], c.395C>T[p.A132V], and c.251G>A[p.R84K] (Table 1). Among these variants, 14 have been previously described, whereas one was a novel variant, c.251G>A[p.R84K], found in dichorionic diamniotic twin babies (S29 and S30). The most common variant observed was c.790G>A[p.R264H] (Table 1). Two patients harbored more than one variant (S25 and S28; Table 1). In the study, 24 out of the 30 infants with PIH had one *MAT1A* gene variant, whereas six infants had compound heterozygous variants in the *MAT1A* gene.

Family Analysis

Family analysis revealed that 30 cases of PIH belonged to 28 families (with S5, 7, and 29 and 30 being siblings). Among the 30 patients with genetically confirmed PIH through *MAT1A* gene analysis, eight of their parents (12 parents) underwent *MAT1A* Sanger sequencing. Four of these parents (S8-1, S19-1, S25-1 and S27-2) were suspected for autosomal dominant inheritance, while two (S18-2 and S26-1) showed autosomal recessive inheritance (Table 1).

Treatment and Outcome

Regarding treatment and outcomes, 24 out of the 30 patients with PIH were initially placed on a low-methionine-formula diet. Seven out of 30 patients continued with a low-methionine diet, including S27, who was only two months old, while 17 discontinued diet treatment, and six of them did not start the low-methionine diet. The average treatment duration for patients on the

Table 3: Initial laboratory and genetic findings in patients with transient hypermethioninemia

S. No	*Gender (F/M)*	*Age at diagnosis (days)*	*NST (µmol/L) Methionine*	*Plasma (µmol/L) Methionine*	*Last follow-up (îmol/L)*		
					Homocysteine (µmol/L)	*Methionine (µmol/L)*	*Homocysteine (µmol/L)*
1	M	59	141.47	194.36	41	51.28	7.56
2	M	475	175	175	103.9	103.9	5.58
3	M	13	81.06	127.03	109	225	10.82
4	M	189	155	120	107	120	8.04
5	F	18	132.63	94.15	62	123.7	0
6	M	72	114.95	139.4	61	139.4	0
7	M	63	359	280	113	280	7.92
8	M	32	64.3	91.2	37.6	91.2	8

Table 4: Mean values of plasma methionine and homocysteine in differential diagnosis

	Initial screening (SD)		*Last follow-up (SD)*	
	Methionine (µmol/L)	*Homocysteine (µmol/L)*	*Methionine (µmol/L)*	*Homocysteine (µmol/L)*
Isolatedhypermethioninemia	248.3 (252.9)	2.2 (5.4)	132.8 (206.8)	1.6 (4.1)
Homocystinuria	903.5 (406.4)	153.5 (77.5)	NA	NA
Transienthypermethioninemia	152.6 (58.7)	79.3 (30.1)	141.8 (69.8)	6.0 (3.7)

low-methionine diet was 50.2 months (range: 2-216 months). Most patients with PIH displayed no clinical symptoms associated with MAT I/III deficiency. Clinical evaluation based on medical record review, developmental milestones, and neurological examinations during follow-up indicated normal development in the majority of patients. Standardised cognitive or IQ testing, when available, further supported the absence of neurological impairment. Only one child (S1) demonstrated mild intellectual disability with an IQ of 66.

DISCUSSION

In this report, the researchers provide a comprehensive analysis of PIH identified through NBS over a 20-year period at a single centre in Korea. Methionine served as the primary biomarker in NBS, enabling the identification of various inborn error of metabolism, most notably MAT I/III deficiency, as well as conditions such as CBS , GNMT deficiency (Chien et al. 2005; Zhao et al. 2022). A key finding of the study is that MAT I/III deficiency caused by variants in the *MAT1A* gene was the predominant etiology of PIH, which is consistent with previous reports (Oh et al. 2010; Chien et al. 2015; Yamada et al. 2020). In particular, heterozygous c.790G>A [p.R264H] was the most frequent variant. This variant exerts a dominant-negative effect while permitting residual enzyme activity, explaining the moderate methionine elevations and relatively benign phenotype.

Only one patient (S1) with very high methionine (981.93 umol/L) developed neurological impairment, aligning with previous reports that extremely elevated levels may predispose to central nervous system (CNS) complications (Zhao et al. 2022). Recent studies have shown the significant impact of methionine metabolism. Methionine is a precursor of S-adenosylmethionine (SAM), a vital metabolite essential for myriad biological processes, including brain cell myelination. Changes in SAM levels have been intricately linked to neurological conditions such as depression, Alzheimer's disease, and spinal cord regression (Bjørke-Monsen et al. 2022; Furujo et al. 2012).

The clinical spectrum of MAT I/III deficiency continues to evolve as newborn screening programs expand and more patients are identified. While the dominant form of PIH due to heterozygous *MAT1A* variants is generally considered benign (Sen et al. 2019), recent evidence suggests that autosomal recessive MAT I/III deficiency can lead to significant neurological consequences. Ma et al. (2024) reported that among 15 patients with recessive MAT I/III deficiency, 66.7 percent exhibited neurological abnormalities including white matter demyelination, with pre-treatment methionine concentrations significantly higher in affected patients. These findings highlight the phenotypic heterogeneity of MAT I/III deficiency and the importance of distinguishing between dominant and recessive forms. In this context, the study provides valuable real-world data on the predominantly favourable clinical course of PIH identified through NBS over two decades in the Korean population, and may serve as an important reference as the number of infants referred for elevated methionine continues to increase worldwide.

The differential diagnosis of hypermethioninemia is crucial. Distinguishing PIH from homocystinuria is essential, as the latter requires an immediate methionine-free diet to prevent neurologic damage (Durand et al. 2001; Enokizono et al. 2023; Zigman et al. 2021). Interestingly, all patients categorised as having transient hypermethioninemia in the cohort exhibited persistent moderate to severe hyperhomocysteinemia (Table 3). This suggests that some may represent undiagnosed or atypical disturbances in homocysteine metabolism, possibly influenced by folate or vitamin B12 deficiency (Villani et al. 2019).

This retrospective study has several limitations. The nationwide NBS for homocystinuria was introduced in South Korea in 2006 and relied on methionine rather than homocysteine measurement, which could have delayed or missed diagnoses requiring prompt methionine free diet initiation. In addition, as a single-centre retrospective study, potential selection bias and restricted generalisability must be considered. Finally, the modest sample size may not fully reflect the clinical and genetic spectrum of hypermethioninemia in the broader population (Martín Rivada et al. 2022).

This study underscores the importance of NBS in detecting isolated hypermethioninemia and homocystinuria, as well as the value of *MAT1A* variant analysis in clarifying inheritance patterns. Most individuals with PIH showed

normal neurological outcomes without dietary therapy, with only markedly elevated methionine associated with complications. Therefore, the main rationale for a low-methionine diet is to mitigate methionine toxicity, while avoiding further SAM depletion (Enokizono et al. 2023). Taken together, the findings highlight that PIH should be regarded predominantly as a biochemical phenotype rather than a clinical disorder in the vast majority of affected individuals, regardless of dietary intervention. Neurologic manifestations were absent except in a single case with extreme methionine elevation, emphasising that PIH generally does not confer clinically significant neurologic risk. Continued monitoring and long-term follow-up essential, and further research with expanded screening will improve clinical strategies for hypermethioninemia.

CONCLUSION

This study presents the clinical and genetic characteristics of persistent isolated hypermethioninemia (PIH) based on a 20-year experience at a single tertiary centre in Korea. *MAT1A* variants were identified in all 30 PIH patients, with 15 distinct variants including one novel variant (p.R84K). The majority of PIH patients demonstrated a favourable clinical course without neurological complications, supporting the notion that PIH predominantly represents a biochemical phenotype rather than a clinically significant disorder. These findings highlight the value of combining newborn screening with MAT1A genetic analysis for the accurate diagnosis and classification of hypermethioninemia.

RECOMMENDATIONS

In clinical practice, when elevated methionine levels are detected through newborn screening, classical homocystinuria should be promptly excluded by measuring plasma homocysteine levels, as it necessitates urgent dietary intervention. Following this, *MAT1A* gene analysis should be performed to confirm PIH and determine the inheritance pattern. This stepwise diagnostic approach is essential for appropriate patient management. Although the present study suggests a generally benign prognosis for PIH, larger multicentre studies with extended follow-up are warranted to further define the long-term outcomes associated with specific MAT1A variants and to establish standardised monitoring guidelines.

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