Mild Persistent Isolated Hypermethioninemia Identified through Newborn Screening in Michigan

Kuntal Sen^{1,2} Michael D. Felice² Allison Bannick¹ Roberto Colombo³ Robert L. Conway^{1,2}

¹Division of Genetic, Genomic and Metabolic Disorders, Children's Hospital of Michigan, Detroit, Michigan, United States

²Wayne State University School of Medicine, Detroit, Michigan, United States

³Center for the Study of Rare Inherited Diseases (CeSMER), Niguarda Ca' Granda Metropolitan Hospital, Milan, Italy

Address for correspondence Kuntal Sen, MD, Division of Genetic, Genomic and Metabolic Disorders, Children's Hospital of Michigan/ Detroit, MI, United States (e-mail: ksen@dmc.org).

J Pediatr Genet 2019;8:54–57.

Abstract

Keywords

- newborn screening
- persistent isolated hypermethioninemia
- *MAT1A* mutation

Methionine S-adenosyltransferase deficiency, due to mutations in *MAT1A*, is the most common cause of persistent isolated hypermethioninemia (PIH). While the recessive form may cause neurological consequences, the dominant form is typically benign. This condition may be found in asymptomatic infants through newborn screening programs. We describe 16 asymptomatic individuals with PIH. Our data reiterates the benign nature of PIH and reports two novel mutations in the gene. There were a disproportionate number of individuals with African descent in this cohort.

Introduction

In 1951, Cantoni described the function of methionine adenosyltransferase (MAT). This enzyme catalyzes the transfer of the adenosyl moiety of ATP (adenosine triphosphate) to methionine which forms S-adenosylmethionine (AdoMet).¹ AdoMet is the principal molecule involved in methyl group transfer in several biological reactions. The gene that codes for the two isoforms of the enzyme MAT I/III is *MAT1A*. The phenotypic spectrum of MAT I/III deficiency is broad ranging from a demyelinating disorder of the central nervous system and variable neurologic sequelae to persistent isolated hypermethioninemia (PIH) in otherwise asymptomatic individuals.² *MAT1A* mutations can be both recessive and dominant, with the latter probably being a benign disorder causing mild to modest methionine elevations and without risk of neurologic symptoms compared with the recessive type, which is associated with severe methionine elevations often > 800 to 1000 µmol/L and variable risk of neurologic symptoms.³ A specific heterozygous *MAT1A* mutation, c.791G>A (p.Arg264His), has been reported as being particularly associated with the dominant form of PIH. An elevated methionine level on newborn screening (NBS) dried blood spot (DBS) analysis typically raises clinical concern for

either homocystinuria (HCU) or MAT deficiency. In addition to these two conditions, there are diagnoses such as tyrosinemia, citrin deficiency, S-adenosylhomocysteine hydrolase deficiency, glycine N-methyltransferase deficiency, as well as liver disease which can also cause hypermethioninemia. We present the follow-up data of 13 infants identified through newborn screening due to elevated methionine and describe the clinical, molecular, and biochemical findings of this cohort. In addition, similar results from two children and one adult from Italy are also described.

Methodology

The present study was performed after obtaining institutional review board approval. To characterize the clinical data of patients identified with PIH, we performed a retrospective chart review of abnormal NBS results for increased methionine identified through the Michigan NBS program over a 10-year period (2005–2015). When reviewing methionine values from our NBS laboratory, it is important to note that the cut-off value for abnormal results changed in 2011 from 74 to 56 µmol/L due to a change in testing method. Infants with elevated methionine levels were referred to our institution's metabolic clinic

received

December 28, 2018

accepted

February 8, 2019

published online

March 27, 2019

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DOI <https://doi.org/10.1055/s-0039-1683900>.
ISSN 2146-4596.

for further testing and management. Confirmatory testing of these infants routinely included quantitative plasma amino acids, and plasma total homocysteine. S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) testing, as well as parental biochemical testing, was not systematically performed. This is a limitation of this report, as that information could help with interpretation of the infant's elevated methionine level. A designation of PIH was given to infants who had at least three elevated methionine levels between the newborn screen and plasma amino acids. Our center serves as the metabolic referral center for infants from anywhere in the state of Michigan. Therefore, some of the laboratory reference ranges are different, as the laboratories where confirmatory plasma amino acids were performed could vary. Information regarding demographics, clinical parameters, biochemical, and molecular test results were collected by reviewing available medical charts. Similar data of two siblings (patients 15 and 16) and their mother (patient 14) were contributed from Italy.

Results

Of the 51 Michigan infants who had an elevated methionine on the NBS specimen, three cases of HCU and 13 cases of PIH were identified; plasma methionine levels normalized on confirmatory plasma amino acid testing in the remainder. Among the PIH cohort (►Table 1), the average methionine level on the NBS was 83.1 $\mu\text{mol/L}$ (range, 60–121 $\mu\text{mol/L}$; reference < 56 $\mu\text{mol/L}$ prior to 2011 and < 74 in 2011 and after). On confirmatory plasma amino acid analysis methionine averaged 118.5 $\mu\text{mol/L}$ (range, 76–419 $\mu\text{mol/L}$; reference ranges varied but all were 65 $\mu\text{mol/L}$ or less). Methionine levels averaged 104 $\mu\text{mol/L}$ on subsequent follow-up (range, 67–173 $\mu\text{mol/L}$; reference ranges varied but all were 65 $\mu\text{mol/L}$ or less). All patients with multiple measurements of plasma amino acids exhibited a plasma methionine trend characterized by an initial postnatal increase and subsequent decrease, a phenomenon previously reported in another study.⁴

In all six patients who received molecular testing, a heterozygous mutation in *MAT1A* was identified. The remainder did not receive genetic testing because they were either lost to follow-up or because the insurance denied coverage of the test, which is a limitation of our report. However, individuals with autosomal recessive MAT deficiency typically have methionine levels elevated much higher (> 200 $\mu\text{mol/L}$) than those of our cohort.⁵ Of note, one patient did not receive genetic testing though her half sibling was identified with a mutation, and they had similar elevations of methionine, implying identical variant genotypes. Three *MAT1A* sequence alterations were identified among our cohort: c.259C>T (p.Arg177Trp) (a previously reported mutation, $n = 3$), along with two novel variants, c.763C>T (p.Pro255Ser) ($n = 1$) and c.839G>T (p.Gly280Val) ($n = 2$). The classification of these new variants as pathogenic is based on biochemical studies showing mild elevations in methionine. The most definitive functional study to establish the pathogenicity of the variants would be measur-

ing MAT activity in liver extract. However, this test is not widely available in the clinical setting. Clinically significant hyperhomocysteinemia was not observed in our cohort (highest measured level was 11 $\mu\text{mol/L}$).

All patients were seen in our clinic for an initial consultation, and the nature of mildly elevated methionine levels was discussed with them. No dietary restrictions or use of AdoMet supplementation was recommended. It was recommended that these infants be followed by a health care provider for growth and development surveillance and to have periodic check of plasma methionine levels. Families were given the option to continue follow-up with our clinic for this, or to have their primary care provider (PCP) to complete the monitoring and report to us any health concerns or rising of methionine levels. All families chose to follow-up with their PCP. All of our patients were followed up in our clinic for an average period of 5.3 months, and a range of 1 to 15.2 months. None of them demonstrated any other neurologic signs reported in the recessive form of MAT I/III deficiency, supporting the observations made by other authors that PIH due to heterozygosity for *MAT1A* mutations represents a benign condition. We have not received any communication from a PCP with a health concern. Time of direct follow-up of our cohort is limited, and a follow-up survey to PCP offices to assess their current growth and development status is a strong consideration to add to longitudinal data about individuals with PIH.

Interestingly, 10 of the 13 patients (77%) from Michigan were African American, although the African American demographic only represented 13.4% of births in Michigan within this same time period.⁶ All patients for whom we had molecular results were of African American descent. This suggests the possibility that the prevalence of heterozygous *MAT1A* mutations causing PIH may be more frequent among this population.

The data from the patients in Italy included two siblings who had PIH (►Table 1, patients 15 and 16). These two brothers were of African origin and were 7 and 5 years at the time of testing. Their plasma methionine levels at diagnosis were 68 and 81 $\mu\text{mol/L}$ (reference, 10–50 $\mu\text{mol/L}$), while their subsequent methionine levels ranged from 58 to 144 and 75 to 159 $\mu\text{mol/L}$, respectively. Identical to our cohort, neither of them had any developmental delays or other neurological issues. Their mother, 27 years old and also asymptomatic, was subsequently ascertained and found to have PIH with a methionine level of 74 $\mu\text{mol/L}$. They all carried the above-mentioned c.763C>T (p.Pro255Ser) *MAT1A* variant.

Discussion

Similar to data published from other NBS programs, the Michigan program identifies mild PIH far more frequently than HCU or MAT deficiency after an increased methionine on the newborn screening test.⁷ Our study found that mild PIH identified through NBS in absence of hyperhomocysteinemia is most frequently caused by heterozygous sequence alterations in *MAT1A*. In the past 15 years, there have been more reports of individuals with dominant PIH compared

Table 1 Clinical, biochemical, and molecular characterization of 16 patients with PIH

Patient	Ethnicity	Sex	NBS results: methionine $\mu\text{mol/L}$	Confirmatory laboratories: methionine $\mu\text{mol/L}$	Follow-up laboratories: Methionine $\mu\text{mol/L}$	Molecular results	Length of follow-up with no clinical concerns (days)
1	Irish, German	F	111 (nl < 74)	97 (10–60)	72–152	Not done	202
2 ^a	African American	F	84 (nl < 74)	90 (10–60)	42–131	Not done	383
3 ^b	African American, Mexican	F	74 (nl < 74)	96 (10–60)	96–134	Not done	29
4 ^b	African American, Mexican	F	89 (nl < 74)	68 (10–60)	68–163	<i>MAT1A</i> : p.Gly280Val heterozygous	107
5 ^a	African American	F	103 (nl < 74)	182 (10–60)	92–182	Not done	457
6	German, French, Scottish	F	70 (nl < 56)	66 (< 56)	66–94	Not done	37
7	African American	M	64 (nl < 56)	70 (10–60)	67–109	<i>MAT1A</i> : p.Arg177Trp heterozygous	146
8	Italian, Irish, Polish	M	71 (nl < 56)	78 (10–60)	78–100	Not done	44
9	African American	M	71 (nl < 56)	124 (10–60)	87–124	<i>MAT1A</i> : p.Gly280Val heterozygous	114
10	African American	F	63 (nl < 56)	61 (11–35)	61–145	<i>MAT1A</i> : p.Arg177Trp heterozygous	327
11	African American	M	69 (nl < 56)	98 (10–60)	67–98	Not done	197
12	African American	M	113 (nl < 56)	74 (< 65)	74–96	<i>MAT1A</i> : p.Arg177Trp heterozygous	45
13	African American, Indian	F	60 (nl < 56)	69 (10–60)	69–122	<i>MAT1A</i> p.Pro255Ser heterozygous	128
14 ^c	African	F	N/A	74 (10–50)	64–117	<i>MAT1A</i> p.Pro255Ser heterozygous	27 years
15 ^c	African	M	N/A	68 (10–50)	58–144	<i>MAT1A</i> p.Pro255Ser heterozygous	7 y
16 ^c	African	M	N/A	81 (10–50)	75–159	<i>MAT1A</i> p.Pro255Ser heterozygous	5 y

Abbreviations: F, female; M, male; NBS, newborn screening.

^aFull siblings.^bHalf siblings.^cPatients from Italy.

with recessive PIH.^{4,5,8–10} Literature review showed nearly 40 individuals who all carried the heterozygous *MAT1A* mutations leading due to benign PIH without any clinical repercussions.^{4,9} Most of these individuals have been reported to have a heterozygous c.791G>A (p.Arg264His) mutation in *MAT1A*, which was not present in our patients. The two novel *MAT1A* sequence changes c.763C>T (p.

Pro255Ser) and c.839G>T (p.Gly280Val) identified in our cohort expands the genotypic spectrum of heterozygous alterations in this gene associated with mild PIH. One of these novel variants, c.763C>T (p.Pro255Ser), was also found in African siblings and mother from Italy. The c.259C>T (p.Arg177Trp) mutation which was present in three of our patients, has been suspected as a pathogenic variant in two

patients in another case series, though that report does not precisely record the inheritance pattern or the clinical significance of this change within their cohort.¹⁰ Although we acknowledge that our genotyping data are limited due to the fact that not all patients in our cohort received molecular testing, we observe that mild PIH due to *MAT1A* heterozygosity appears to be more common among individuals of African descent in our state's newborn screening of population. The findings of this publication represent the outcomes of a public health program and not a research initiative.

Conclusion

Our data support the observation that mild PIH associated with *MAT1A* heterozygosity appears to be a benign disorder that does not require treatment. *MAT1* heterozygosity, along with other serious disorders that can cause hypermethioninemia can be found through NBS. Therefore, confirmatory testing including molecular analysis should be completed for all such cases. If a case is proven to be a result of *MAT1A* heterozygosity, routine follow-up might be unnecessary and can be considered incidental finding. We are also reporting two new variants in *MAT1A* gene and postulate that this biochemical phenotype may be more common among individuals from certain African populations.

Conflict of Interest

None declared.

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