Thirteen Patients with *MAT1A* Mutations Detected Through Newborn Screening: 13 Years' Experience

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Abstract

Background: Methionine adenosyltransferase I/III (*MATI/III*) deficiency is the most common genetic cause of persistent isolated hypermethioninemia.

Patients and Methods: This is a retrospective data analysis of 62 newborns with elevated methionine detected by newborn screening between January 2000 and June 2013. The clinical, biochemical, and molecular findings of a subset of these children with *MAT1A* mutations associated with *MATI/III* deficiency are presented.

Results: Of the 62 newborns with elevated methionine, 12 were identified as having classical homocystinuria; 37 were false-positives; and 13 were found to have isolated persistent hypermethioninemia in the absence of biochemical markers of homocystinuria, abnormal liver function studies, or other causes of elevated methionine. These 13 individuals underwent genetic testing for changes in the *MAT1A* gene, associated with *MATI/III* deficiency. Three of 13 were found to have the common autosomal dominant R264H mutation, one was found to be a compound heterozygote for two novel pathogenic mutations, and three were found to be heterozygotes for previously reported mutations shown to cause autosomal recessive *MATI/III* deficiency when present in homozygous or a compound heterozygous configuration. The remaining six patients had variants of unknown clinical significance or novel mutations. For the majority of individuals, methionine persisted

above the normal range but trended downward over time. None of these 13 individuals was started on a low-methionine diet, and all have age-appropriate growth and development.

Conclusion: These cases show that individuals with even single changes in the *MAT1A* gene may have elevations in methionine identified by newborn screening, which may persist for months after birth without any clinical consequences.

Introduction

Methionine adenosyltransferase I/III (*MATI/III*) deficiency is the most common genetic cause of persistently elevated methionine (Couce et al. 2008). Following the introduction of methionine into newborn screening programs to detect newborns with homocystinuria due to cystathionine beta-synthase (CBS) deficiency, a subset of children with persistently elevated methionine but with normal homocysteine levels were detected. No known molecular reason for their metabolic abnormalities was evident (Mudd et al. 1995). Subsequent investigation identified the cause of elevated methionine to be due to a deficiency of methionine adenosyltransferase, expressed in the liver, which is encoded by the *MAT1A* gene (Ubagai and Lei 1995). Following the discovery of this enzyme deficiency and gene, it was noted that there were two main inheritance patterns for this condition: (1) a less common autosomal recessive form, which in addition to persistently elevated methionine, in some cases, is also characterized by developmental delay and progressive brain demyelization, and (2) an autosomal dominant form, characterized by the R264H mutation, which is clinically benign (Mato et al. 2001; Ubagai and Lei 1995; Chamberlin et al. 1997, 2000).

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Since 1995, 37 mutations in the *MAT1A* gene have been described in patients with MATI/III deficiency (Mudd 2011).

In this report, we discuss 13 newborns with elevated methionine levels detected through newborn screening, subsequently found to have mutations in the *MAT1A* gene. This represents the largest report of trends among individuals identified through newborn screening in the United States who have *MAT1A* mutations, many without the common R264H autosomal dominant mutation.

Patients and Methods

A retrospective chart review was conducted from January 2000 to June 2013 to identify all newborns referred to our center for elevated methionine identified on newborn screening. Eligible patients' records were reviewed, and biochemical laboratories, developmental status, and genetic test results were compiled for comparison. Patients are indicated by letter and number, the number corresponding to the order of which individuals in a single family were referred for evaluation.

Results

Sixty-two newborns with positive newborn screenings for elevated methionine came to the Children's Hospital of Philadelphia from January 2000 to June 2013. Our referral area includes the newborn screenings from the states of Pennsylvania, Delaware, and New Jersey. Methionine cut-offs for these states are <0.80 mg/dL (<53.6 μ mol/L), <45.0 μ mol/L, and <0.80 mg/dL (<53.6 μ mol/L), respectively.

All 62 newborns were evaluated at our center within the first 6 weeks of life to assess for an inborn error of metabolism responsible for the observed elevated methionine. Of the 62, 37 (59.7 %) were found to be false-positives and had no further elevation of methionine or other metabolites outside of the normal range. Twelve (19.3 %) were found to have CBS deficiency and were subsequently managed. The remaining 13 (20.9 %) were found to have persistently elevated methionine with normal or modest levels of total homocysteine and free homocysteine, normal liver function studies, and no other observed cause for elevated methionine. Of note, the modest elevations in methionine were lower than the expected values for an infant with CBS deficiency. Of the 13, three sibling pairs were identified (patients B1, B2; C1, C2; D1, D2).

Of the 13 cases with persistently elevated methionine, the initial methionine level identified on newborn screening was not predictive of MATI/III deficiency, false-positives,

or classical homocystinuria. All of the infants were either receiving breast milk, standard formula for infants, or a combination of the two. No infants received any specialized metabolic formulas. Eleven of 13 infants also had liver enzymes analyzed at their first clinical evaluation to assess for liver dysfunction as a cause for elevated methionine. Liver enzymes showed clinically unremarkable findings in all cases. See Table 1 for the initial screening and clinical labs.

Subsequent to the identification of persistently elevated methionine, genetic testing was performed to determine if MATI/III mutations could be identified to explain their biochemical profile. In all patients, at least one variant or mutation was identified in the *MAT1A* gene. Table 2 presents a summary of these findings.

Following the identification of elevated methionine and mutations/variants in the above patients, it was recommended that these patients continue to follow-up in our clinic for regular monitoring of methionine levels. A summary of the number of clinical evaluations and average methionine levels for these 13 patients can be seen in Table 1. All patients described in this series had average methionine levels higher than the normal range. However, for the majority of patients, these levels have fallen over time. The trends of the patients' methionine levels can be seen in Fig. 1.

To date, all patients described have had normal development by parental report and are meeting milestones at an age-appropriate level. All patients are eating a diet typical for a child their age.

Discussion

The majority of individuals with MATI/III deficiency have been identified through newborn screening programs. Several papers report their experience in the identification and treatment of these individuals, although the majority of these patients have been found to have the R264H autosomal dominant mutation or known autosomal recessive mutations (Couce et al. 2013; Chien et al. 2005; Couce et al. 2008; Martins et al. 2012). In 2013, Couce et al. described 18 patients identified in newborn screening programs in Spain with MATI/III deficiency, 15 of which had the R264H mutation. Follow-up data were also reported for these patients and similarly shows that even in individuals without clinical features, methionine levels continue to remain elevated. Mean values of methionine are only presented, however, and trend data is not available (Couce 2013). In 2005, Chien et al. described 16 individuals with hypermethioninemia identified through neonatal screening in Taiwan over a 12-year time period. Of these, nine had mutations in the *MAT1A* gene, four had

Table 1 Initial screening and biochemical values and mean methionine values for patients and with persistently elevated methionine first identified on newborn screening

Patient	State	Age at first visit (weeks)	Breast milk/Formula	Met levels – NBS (nmol/mL)	Met levels – First visit (nmol/mL)	Initial tHcy (umol/L)	Initial ALT (U/L)	Initial AST (U/L)	Mean Met (nmol/mL)	Age at last Eval (months)
A1	PA	3	Formula	42.9	80.8	4.7	33	64	80.8 (1)*	0.67
B1	NJ	6	Formula (Enfamil with Iron)	195.0	218.9	15.04 (H)	35	25	218.9 (1)*	1.3
B2	NJ	2	Breast Milk, Formula Supplement (Enfamil with Iron)	126.0	232.8	7.8	30	25	258.76 (11)*	37.2
C1	PA	3.5	Formula (Carnation Good Start)	99.9	181.1	10.64	<6	43	87.2 (3) *	29.0
C2	PA	6	Formula (Carnation Good Start)	42.9	523.2	18.8 (H)	7	47	285.6 (2)*	10.6
D1	PA	5	Formula (Enfamil with Iron)	64.3	209.8	9.71	n/a	n/a	138.8 (5)*	16.2
D2	PA	4	Formula (Carnation Good Start)	64.3	112.8	n/a	n/a	n/a	88.75 (2)*	5.1
E1	NJ	2	Breast Milk	86.5	406.4	13.57	35	91	298.5 (4)*	8.4
F1	PA	2	Formula (Similac/Carnation Good Start)	70.4	88.9	5.76	39	28	63.4 (5) *	24.3
G1	PA	2	Breast Milk, Formula Supplement	52.9	84.8	6.23	22	56	76.2 (5)*	16.1
H1	DE	4	Formula (Similac Advance)	71.5	235.5	9.36	8	106	244.94 (5) *	6.9
I1	PA	3.5	Breast Milk	64.3	80.00	6.95	33	61	63.1 (3)*	4.8
J1	PA	2.7	Formula (Carnation Good Start Gentle)	47.6	114.3	4.32	23	91	97.5 (2)*	2.5

Met Methionine, tHcy total homocysteine, ALT Alanine transaminase, AST Aspartate aminotransferase

(*) number of measurements of plasma methionine

Table 2 Variant/Mutations observed in 13 patients with persistently elevated methionine

	Genotype	Genotype information
A1	R219L	Novel – Variant of Unknown Clinical Significance
B1	R264H	Reported Previously – Autosomal Dominant (Mato et al. 2001)
B2	R264H	Reported Previously – Autosomal Dominant (Mato et al. 2001)
C1	A55D	Reported Previously – Autosomal Recessive (Ubagai and Lei 1995)
C2	A55D	Reported Previously – Autosomal Recessive (Ubagai and Lei 1995)
D1	A259V	Reported Previously – unclear inheritance pattern (Fernandez-Irigoyet et al. 2010)
D2	A259V	Reported Previously – unclear inheritance pattern (Fernandez-Irigoyet et al. 2010)
E1	I37T/G91S	Novel – Suspected Pathogenic Novel – Suspected Pathogenic
F1	R177W	Novel – Suspected Pathogenic
G1	M138V	Novel – Variant of Unknown Clinical Significance
H1	R264H	Reported Previously – Autosomal Dominant (Mato et al. 2001)
I1	P357L	Reported Previously – Autosomal Recessive (Ubagai and Lei 1995)
J1	R177W	Reported Previously (see patient F1) – unclear inheritance pattern

at least one copy of the known autosomal recessive R264H mutation, two were compound heterozygotes for known autosomal recessive mutations, and the remaining three were heterozygotes or compound heterozygotes for novel mutations that were suspected to be pathogenic. The majority of patients were put on a restricted diet, and all individuals were reported to have normal growth, development, and neurological examinations (Chien et al. 2005). In 2008, Couce et al. described five individuals with MATI/III deficiency identified over 7 years' time through newborn screening in Galicia, Spain. All five patients were heterozygotes for the R264H autosomal dominant mutation and were kept on diets not exceeding recommended protein requirements for their age. At the time of publication, with a mean of 2.5 years of clinical follow-up, all individuals were asymptomatic (Couce et al. 2008). Finally, in 2011, Martins et al. reported 11 cases of MATI/III deficiency identified through the Portuguese Newborn Screening Laboratory. All cases reported were heterozygotes for the R264H autosomal dominant mutation. All individuals had normal development; however, one patient was found to have myelination abnormalities of unknown clinical significance (Martins et al. 2012).

Our report is the first that focuses on the trend of methionine levels in individuals with *MAT1A* mutations other than the common R264H autosomal dominant mutation. The majority of patients in this case report are heterozygotes for known autosomal recessive mutations, variants of unknown clinical significance, or reported mutations with unclear inheritance patterns. The majority of individuals in this study presented with methionine levels that trended downward upon follow-up. None of the individuals reported in this series have had any symptoms of MATI/III deficiency. All patients have normal develop-

ment and tolerate diets typical for other infants and children their age.

Of note, three sibling pairs were identified in this study, B1 and B2, C1 and C2, and D1 and D2. B1 and B2 are heterozygotes for the common R264H mutation and are difficult to compare because B1 has only had one clinical evaluation to date. Patients C1 and C2, heterozygotes for the A55D autosomal recessive mutation, exhibit a similar trend of methionine, with both falling substantially over time and eventually falling within the normal range. The values, however, differ drastically. As observed in Table 1 and Fig. 1, C2's initial methionine level is nearly double that of C1. Similarly, siblings D1 and D2, despite having identical mutations, have varying patterns of methionine. As shown in Fig. 1, D1's levels fell sharply following initial presentation, rose again, and have relatively leveled off, still above the normal threshold for methionine levels. Patient D2, however, showed a sharp decrease and is near the upper limit of normal for methionine levels.

Thus, we conclude the following from this report: (1) Our data shows that newborns with single *MAT1A* mutations other than the common R264H mutation can present with elevated methionine levels and be detected by newborn screening and, if followed over time, will continue to have methionine elevations outside the normal range. (2) Although increased methionine levels persisted for months after birth, none of the patients had any clinical symptoms or developmental delay. (3) Siblings with identical mutations or variants in the *MAT1A* gene do not have identical trends of methionine levels, which may reflect different methionine intake in diet or could suggest that there may be other modifier genes that influence methionine values. (4) Clinicians who evaluate patients following positive newborn screenings for methionine should be aware that

Fig. 1 Methionine trends in patients with MATIA mutations. **(a)** Data for sibling pairs. **(b)** Data for non-siblings

isolated persistent elevation of methionine could be caused by single mutations in the *MATIA* gene. (5) Increasing cut-off values for methionine may impede detection of newborns carrying benign mutations in the *MATIA* gene. However, to ensure that no cases of CBS deficiency are missed, homocysteine should also be introduced into newborn screening panels.

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