Case Report

The biochemical profile and dietary management in S-adenosylhomocysteine hydrolase deficiency

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ABSTRACT

S-Adenosylhomocysteine (SAH) hydrolase deficiency is an autosomal recessive disorder in methionine metabolism caused by pathogenic variants in the gene AHCY. To date, only 15 patients with this disorder have been reported, including several patients treated with dietary management. In this study, we report a new case with SAH hydrolase deficiency and conduct a literature review with a focus on the biochemical profiles and the efficacy of dietary management. The biochemical markers associated with SAH hydrolase deficiency includes elevated levels of methionine, creatine kinase (CK), SAH, and S-Adenosylmethionine (SAM). However, half of the cases (6/12) had normal methionine levels at the initial evaluation. In contrary, SAM and SAH were markedly elevated in all reported patients at the initial evaluation (SAM: range 1.7×–53×, median 21.5×; SAH: range 4.9×–193.8×, median 98.1×). Nine patients were treated with methionine-restricted diet, which markedly reduced SAM and SAH in all patients but the levels did not normalize. CK and liver function did not show significant improvement with dietary treatment. The majority of patients (5/8) demonstrated clinical improvements with dietary management, such as increase in muscle strength; but all patients continued to experience developmental delay and two deaths were reported from cardiopulmonary arrest. This study suggests that methionine is not a reliable diagnostic biochemical marker for SAH hydrolase deficiency and SAM/SAH levels should be considered in the workup in neonates with unexplained hypotonia, liver dysfunction, or elevated CK. Dietary restriction of methionine demonstrates clinical benefits in some affected patients and should be trialed in patients with SAH hydrolase deficiency.

1. Introduction

Methionine is an essential amino acid that serves as the precursor for S-Adenosylmethionine (SAM), which is the principal methyl donor for the methylation of DNA, RNA, protein, lipids, and other biological substrates. SAM is converted to S-Adenosylhomocysteine (SAH) after donating the methyl group in a methylation reaction. SAH hydrolase is a tetrmeric enzyme that catalyzes a reversible reaction to convert SAH to homocysteine and adenosine using NAD+ as a cofactor [1]. Homocysteine is then remethylated to methionine in a cobalamin-dependent process [1]. SAH hydrolase has been shown to have a role in various cellular functions through regulation of methylation reactions, such as epigenetic homeostasis, stem cell proliferation, aging, and circadian clock [2,3]. SAH hydrolase deficiency is a rare autosomal recessive disorder resulted from pathogenic variants in the gene AHCY. Patients with SAH hydrolase deficiency have a broad spectrum of clinical features, including developmental delay, intellectual disability, hypotonia, and early death [4–8]. Affected individuals usually have markedly elevated methionine, SAM, and SAH. Creatine kinase (CK) and liver impairment are also common in patients with SAH hydrolase deficiency [9,10]. Methionine-restricted diet, with or without creatine and phosphatidylcholine supplementation, have been used in several patients [5,11–14]. Due to the rarity of this disorder, the clinical course and underlying pathogenesis of SAH hydrolase deficiency are still largely unknown. In this study, we report a new case of SAH hydrolase deficiency with two novel pathogenic variants. We also analyze the biochemical profiles of 15 reported cases with SAH hydrolase deficiency to assess the efficacy of

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biochemical markers for diagnosis and disease monitoring. In addition, the clinical outcomes of dietary management are examined in treated patients.

2. Patients and methods

This study is conducted retrospectively in compliance with institution’s protocol at the Children’s Hospital of Orange County. The medical history and biochemical data of the proband were retrieved from medical records. A literature search was performed in PubMed and Google Scholar for SAH hydrolase deficiency. Key words used in the literature search includes ‘S-Adenosylhomocysteine hydrolase deficiency’, ‘SAH hydrolase deficiency’ and ‘SAHH deficiency’. A total of 16 patients with SAH hydrolase deficiency including 15 patients identified in literature search are included in this study. The clinical features, biochemical profiles, dietary management, and clinical outcomes are examined for included patients.

The whole genome sequencing was performed at the Rady’s Children Institute of Genomic Medicine (San Diego, CA, USA) using whole blood specimen with an average genomic coverage of 35×.

Fig. 1. Clinical and biochemical profiles of proband.
3. Results

3.1. Case report

The proband male was born at 34 weeks through emergency C-section due to prolonged labor in a pregnancy that was complicated by polyhydramnios and a subchorionic hematoma. Birth parameters were weight 2.39 kg (78th percentile), length 45 cm (66th percentile), and head circumference 33.5 cm (97th percentile). Apgar scores were 6 at 1 min and 8 at 5 min. At delivery, patient was noted to have a tight nuchal cord, weak cry, dusky color, poor tone, and was subsequently intubated due to apnea and desaturations. The methionine was elevated at 123 μmol/L in the initial newborn screening (NBS) collected at DOL1 but did not trigger referral for hypermethioninemia because the patient was on total parenteral nutrition (cutoff <200 μmol/L with TPN). A repeat NBS without TPN was then performed at DOL 13 with a normal result (10 μmol/L, cutoff >6.3 to <89 μmol/L without TPN) and his NBS was reported as negative. Patient was found to have liver dysfunction and generalized hypotonia with markedly elevated CK of 1555 U/L (<355). Patient was suspected to have a congenital muscular dystrophy, and was transferred to our center for further workup at one month of age. Patient was hospitalized for 3.5 months in the neonatal ICU due to respiratory failure and generalized hypotonia requiring tracheostomy and gastrosomy tube placement. At the age of 4 months, a whole genome sequencing revealed two variants of unknown significance in the gene AHCY, which encodes SAH hydrolase. The two variants, c.142G > A (p.Ala48Thr) and c.106C > T (p.Arg36Trp), have not been reported in the past. Given that his clinical features (neurodevelopmental delay and hypotonia) and biochemical profile (markedly elevated CK, transaminases, and hypoalbuminemia) were consistent with SAH hydrolase deficiency, the two novel variants were reported as pathogenic. The diagnosis was then further confirmed by markedly elevated plasma levels of methionine at 292 μmol/L (9–42 μmol/L), SAM at 5030 nM (33–95 nM), and SAH at 3290 nM (13–28 nM) at 4 months of age. Homocysteine levels were repeatedly normal. Methionine-restricted diet, creatine, and phosphatidylcholine supplements were started at the age of 4.8 months. Patient demonstrated clinical improvement in muscle strength and development with dietary management. His growth curve improved from the 50th to the 75th percentile for age after started dietary treatment (Fig. 1A and B). The methionine-restricted diet significantly reduced the levels of methionine, SAM, and SAH but CK and liver transaminases remained elevated (Fig. 1C-H). Patient gradually deteriorated after multiple hospitalizations from recurrent infections and deceased in a cardiorespiratory arrest at the age of 11.8 months.

3.2. Biochemical profiles of SAH hydrolase deficiency

To assess the efficacy of diagnostic markers for SAH hydrolase deficiency, we examined the biochemical profiles in all reported patients in the literature. We identified a total of 16 patients, including the new case in our center. Of them, 12 cases were reported with biochemical profiles. We specifically reviewed the values of methionine, CK, SAM, and SAH as diagnostic markers for SAH hydrolase deficiency. Interestingly, only 33% of patients (3 in 9) had elevated methionine levels at the initial evaluation that occurred within the first two months of life. Meanwhile, all 3 patients who were diagnosed at a relatively later age (8 months or later) had markedly elevated methionine (Table 1). This finding suggests methionine is not a reliable marker to detect SAH hydrolase deficiency in early infancy. Next, we examined the level of CK in patients with SAH hydrolase deficiency because hypotonia is a common feature for SAH hydrolase deficiency and competitive inhibition by SAH on GAMT (guanidinoacetate methyltransferase) results in myopathy [4]. We found that CK was elevated in 78% (7/9) patients with SAH hydrolase at the initial evaluation. We then investigated SAM and SAH as a diagnostic marker for SAH hydrolase deficiency. All patients (8/8) with

### Table 1

Summary of biochemical profiles at initial evaluation in patients with S-adenosylhomocysteine hydrolase deficiency.

| Patient ID | Methionine μmol/L | Creatine kinase U/L | SAM nM | SAH nM |
|-----------|-------------------|---------------------|--------|--------|
| 1*        | NBS 123 (200 on TPN at DOL1) | 1555 U/L (57–374) at DOL6 | 5030 nM (33–95) at 19 weeks of age | 3290 nM (13–28) at 19 weeks of age |
| 2         | NBS normal at DOL1 | N/A | N/A | N/A |
| 3 [13]    | NBS >200 μmol/L (300+) | 1500 U/L (<250) IU/L at 5 months of age | N/A | N/A |
| 4 [11]    | 35 μmol/L (25.4–27.3) at DOL1 | 10,860–16,800 U/L during first 2 weeks of age | 316 nM (164–190) at DOL1 | 279 nM (48–57) at DOL1 |
| 5 [14]    | Normal at DOL3 | 70× of normal at DOL1 | 1.8× of normal at DOL3 | 6.5× of normal at DOL3 |
| 6 [6]     | 273 μmol/L (6–60) at DOL4 | 147 U/L (232) at DOL42 | 2179 nM (77–109) at DOL3 | 2276 nM (20–36) at DOL3 |
| 7 [6]     | 642 μmol/L (<54 μmol/L at DOL18 | 19,89 U/L (<76) at DOL41 | N/A | N/A |
| 8 [9]     | 528 μmol/L (6–60) at DOL3 | 1086 U/L at 8 months of age | 5109 nM (± 28) at 8 months of age | 8139 nM (± 15) at 8 months of age |
| 9 [5]     | 27 μmol/L (12–45) at 2 months of age | 5.88–19.56μkat/ L (<2.72) at 2 months of age | 3.2 μmol/L (0.013–0.141) at 4.5 years of age | 6.8 μmol/L (0.004–0.081) at 4.5 years of age |
| 10 [4]    | 477–784 μmol/L (13–45) at 8 months of age | 2000–4360 U/L (<228) at 8 months of age | 2971 nM (77–109) at 6 months of age | 5044 nM (15–45) at 8 months of age |
| 11 [12]   | 614 μmol/L (22–40) at 8 months of age | 1086 U/L at 8 months of age | 5109 nM (± 28) at 8 months of age | 8139 nM (± 15) at 8 months of age |
| 12 [7]    | 528 μmol/L (6–60) at DOL3 | N/A | N/A | N/A |

References are shown in brackets. * Probands; Guthrie bacterial inhibition assay; DOL day of life.

SAH hydrolase deficiency had elevated SAM and SAH at their initial evaluation but SAH was more elevated than SAM (Table 1). The level of SAM was in average 23.7 times higher than the upper limit of normal range (range 1.7×–53×, median 21.5×) while the level of SAH averaged 87.3× of normal (range 4.9×–193.8×, median 98.1×) at the initial evaluation.

3.3. Dietary management of SAH hydrolase deficiency

Given methionine is the precursor of SAM/SAH, it has been proposed that reduced methionine intake can lead to improved clinical outcomes by decreasing the toxic levels of SAH. To date, nine patients with SAH hydrolase deficiency have trialed a methionine-restricted diet (Table 2). The methionine intake in those patients ranged from 15 mg/kg/day to 40 mg/kg/day through methionine-free formula and low protein diet. The levels of plasma methionine significantly decreased after starting methionine-restricted diet in all patients and normalized in many of them. The levels of SAM and SAH decreased but were still significantly higher than the normal. CK and liver functions did not show significant change with dietary management in all cases. Clinical improvements in muscle strength and mental alertness were reported in 5/8 patients. However, all patients still had developmental delay and two patients died from cardiopulmonary arrest.
Summary of dietary management and outcomes in patients with S-adenosylhomocysteine hydrolase deficiency.

| Patient ID | Starting age for treatment | Dietary regimen | Biochemical improvement | Clinical improvement |
|------------|----------------------------|----------------|-------------------------|---------------------|
| 1*         | 4.8 months                 | Methionine-restricted diet and methionine-free formula at 20-40 mg/kg/d | Improved methionine, SAM, and SAH | Normal growth but myopathy continue to deteriorate, died at day 11.8 months from cardiopulmonary arrest |
| 2 [12]     | 5 months (stopped at 5 years) | Dietary restriction of methionine to 20 mg/kg and protein to 1.0-1.4 g/kg | Methionine normalized | No apparent clinical or behavioral improvement |
| 4 [11]     | 3.5 months                 | Low methionine diet and methionine-free formula at 15 mg/kg/d | Improved methionine, SAM, and SAH | Improve muscle strength and development but still has developmental delay and hypotonia |
| 5 [14]     | 18 days                    | Methionine-restricted diet and phosphatidylcholine and creatine supplement | Improved methionine, SAM, and SAH | Gained strength, became more alert with better contact and spontaneous activity |
| 7 [6]      | 76 days                    | Methionine-restricted diet and methionine-free formula and phosphatidylcholine and creatine supplement | Improved methionine, SAM, and SAH | Continue to deteriorate, died at day 122 from cardiopulmonary arrest |
| 9 [3]      | 4.5 years                  | Methionine-restricted diet 20-25 mg/kg/d | Improved methionine, SAM, SAH, liver function, and coagulation | No major neurological improvement |
| 10 [4]     | 12.8 months                | Methionine-restricted diet at 15 mg/kg/d and phosphatidylcholine supplemented by egg yolk | Improved methionine, SAM, and SAH | Gradual gains in muscle strength and mental responsiveness |
| 11 [12]    | 22 months                  | Methionine-restricted diet ≤35 mg/kg/d and phosphatidylcholine 200 mg/kg/d supplement | Improved methionine, SAM, and SAH | No acceleration in weight gain or head growth |
| 12 [7]     | 7 years                    | Low protein diet at 5-10 g/d | Methionine and transaminases normalized | N/A |

References are shown in brackets. * Proband.

Creatine and choline synthesis are methylation-dependent pathways, which can be inhibited by high level of SAH [12]. In fact, low levels of creatine and choline have been observed in patients with SAH hydrolase deficiency [4]. Given that, phosphatidylcholine and creatine were supplemented in seven patients in addition to methionine-restricted diet. We are unable to assess the specific benefit of phosphatidylcholine and creatine supplementation as all of these patients were also on methionine-restricted diet and there were no significant additional improvements in development or cognitive function following initiation of phosphatidylcholine or creatine.

4. Discussion

SAH hydrolase deficiency is a rare inherited metabolic disorder in the methionine cycle. Pathogenic mutations in SAH hydrolase impair the conversion of SAH to homocysteine and adenosine, resulting in the accumulation of SAH. High cellular level of SAH has been proposed to be the toxic metabolite in SAH hydrolase deficiency because SAH has been shown to inhibit a number of methyltransferases catalyzing important methylation-dependent processes [12]. Clinically, SAH hydrolase deficiency is a disorder with a spectrum of disease severity ranging from death in early infancy to survival into adulthood with relatively mild symptoms. Regardless of the disease severity, most patients with SAH hydrolase deficiency demonstrated three main features: hypotonia, cognitive impairment, and liver dysfunction. Although SAH has been studied for many years at the molecular level, the role of SAH in contributing the phenotypes of SAH hydrolase deficiency has largely been unknown because the rarity of this disorder and the lack of a viable animal model.

Biochemically, marked elevation of SAM and SAH is the hallmark for SAH hydrolase deficiency. However, the levels of SAM and SAH are often not tested in neonates with hypotonia and liver dysfunction because SAH hydrolase deficiency is an extremely rare condition and testing availability is often limited. Newborn screening theoretically can detect SAH hydrolase deficiency from hypermethioninemia. Although SAH hydrolase deficiency is not listed as a disorder in the Recommended Uniform Screening Panel (RUSP) in the US, metabolic referral centers will likely investigate causes of unexplained hypermethioninemia in newborn screening, including SAH hydrolase deficiency and glycine N-methyltransferase deficiency. However, all three cases that had newborn screening in the US, including our case, were negative for hypermethioninemia in the NBS. The low sensitivity makes methionine an impractical marker to be used in newborn screening for SAH hydrolase deficiency. In fact, the levels of methionine are only elevated in 50% of patients (6/12) with SAH hydrolase deficiency at the initial evaluation. The methionine level appears to increase in weeks to months following birth but one patient was reported to have a normal methionine level at two months of age. It is unclear why the methionine levels are not elevated in many SAH hydrolase deficiency patients during early infancy. One possible explanation is that the elevated level of SAM is buffered by GNMT, which converts glycine to sarcosine and prevents rapid accumulation of methionine. Elevated sarcosine levels have actually been reported in patients with SAH hydrolase deficiency [11]. Given that methionine is not a reliable marker for SAH hydrolase deficiency in the neonatal period, the diagnosis of this very rare disorder will require high vigilance in neonates with unexplained liver dysfunction and hypotonia with persistently elevated CK. The levels of SAM, SAH, and/or molecular testing are needed to rule out SAH hydrolase deficiency in suspected cases. The enzyme activity of SAH hydrolase could also be assayed to confirm the diagnosis in a research setting [4].

Homocysteine has been reported to be mildly elevated in four patients with SAH hydrolase deficiency [4,5,7,12]. Interestingly, all elevated homocysteine levels were measured when the patients were at least 8 months old. All reported homocysteine levels were within the...
normal range in patients younger than 8 months of age. It has been proposed that the mildly elevated homocysteine at older age is secondary to the very high levels of methionine in untreated patients. Homocysteine, therefore, cannot be used as a diagnostic marker for SAH hydrolase deficiency.

The etiology of liver dysfunction in this condition is unclear at this time. The evidences are consistent with impaired synthetic function of liver given hypoalbuminemia and coagulopathy. Although no radiographic signs of cirrhosis were reported for this disorder, one case was reported to develop hepatocellular carcinoma at the age of 29 years [7], which suggests possible chronic inflammatory process. Given most patients with this disorder were reported during childhood, long term tumor surveillance may be indicated in surviving patients.

Dietary restriction of methionine is effective in lowering or normalizing plasma methionine, which in term reduces the levels of SAM and SAH, although they remain significantly elevated. Although CK and liver dysfunction does not show improvement with methionine restriction, more than half of the patients demonstrate clinical improvements in muscle strength and perhaps cognitive function. It is still questionable if dietary management is sufficient to alter the disease course or slow the disease progression given two patients on dietary management deceased before one year of age. Nevertheless, dietary management should be tried in patients with SAH hydrolase deficiency since there is no other effective treatment available at this time. The methionine restriction regimens were reported to range from 15 mg/kg/d to 40 mg/kg/d. Although the minimum safe level of methionine intake in infants and young children is 15–20 mg/kg/d per World Health Organization, most patients with SAH hydrolase deficiency had a daily methionine intake from 20 to 40 mg/kg/d, which has effectively lowered the methionine level to the low normal range. A more restricted dietary regimen could further impair the synthetic function of liver and has not shown to provide additional benefits. Interestingly, one patient received liver transplant after ineffective dietary management and have shown some promising improvements not only in biochemical markers but also in clinical symptoms 6 months after the transplant [12]. A longer follow up and more cases will be needed to assess the benefit of liver transplant for SAH hydrolase deficiency.

The growth curve for height and weight are shown in A and B respectively. The trend of plasma methionine (C), CK (D), SAM (E), SAH (F), ALT (G), and albumin (H) are plotted longitudinally. The upper and lower limit of reference ranges are shown in each panel. Black arrow indicates the starting time for dietary treatment.

Data availability

The data that has been used is confidential.

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