Potential Misdiagnosis of Hyperhomocysteinemia due to Cystathionine Beta-Synthase Deficiency During Pregnancy

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Abstract Extreme hyperhomocysteinemia with low cystathionine and cysteine is virtually diagnostic of cystathionine beta-synthase (CBS) deficiency since remethylation defects and hypermethioninemia due to other inborn errors cause elevated serum cystathionine. However, a pregnant CBS deficient patient was found to have elevated cystathionine in addition to elevated total homocysteine and methionine at 23 weeks of gestation and post-delivery cystathionine decreased to the lower level of normal. A second patient with cystathionine values during gestation also showed a rise from the low pre-pregnant value to massive elevation by delivery. Her infant had severe hyperhomocysteinemia in cord blood with a massive elevation of cystathionine, S-adenosylmethionine, and S-adenosylhomocysteine. The infant corrected her homocysteine value by 2 months and is not affected. This data demonstrates that the fetus when exposed to high homocysteine and methionine has increased synthesis of cystathionine which cannot be cleared because the fetus lacks cystathionine gamma-lyase, and thus cystathionine is returned to the mother's circulation. This situation could lead to a misdiagnosis of the cause of hyperhomocysteinemia in a previously undiag-

nosed pregnant CBS deficient patient. Assays combining homocysteine with cystathionine measurements are commonly available from commercial laboratories in the USA. The recognition of CBS deficiency vs. remethylation disorders is important in order to maximize treatment. The cord blood values revealed a major disturbance in methionine metabolism including a potential for impaired transmethylation reactions in the fetus due to the buildup of S-adenosylhomocysteine. It is possible that monitoring maternal cystathionine during gestation could provide another measure of fetal exposure to homocysteine.

Introduction

Severely elevated homocysteine (tHcy) with low cystathionine and low cysteine is virtually diagnostic of cystathionine beta-synthase (CBS) deficiency (classical homocystinuria) since remethylation defects and hypermethioninemia due to other inborn errors cause elevated serum cystathionine and normal cysteine concentrations (Orendac et al. 2003; Stabler et al. 2013; Bártl et al. 2014) (Fig. 1a–c). We report the presence of elevated serum cystathionine during pregnancy in two patients with CBS deficiency. This demonstrates that elevated cystathionine with hyperhomocysteinemia might lead to misdiagnosis of a remethylation disorder rather than classical homocystinuria. Severe hyperhomocysteinemia is a well-documented cause of thrombosis, and pregnancy is a high-risk condition for thrombotic disease. Measuring homocysteine is often part of routine testing for causes of

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Fig. 1 Pathways of homocysteine and methionine metabolism. **(a)** Homocysteine is either remethylated to methionine by methionine synthase (MS) utilizing methylcobalamin (Me-Cbl) and N⁵-methyltetrahydrofolate (Me-THF) as co-factors, or it is condensed with serine (not shown) to form cystathionine by cystathionine beta-synthase (CBS) which uses pyridoxal phosphate (B₆) as a cofactor. Cystathionine is converted to cysteine by cystathionine gamma-lyase (CGL) in another pyridoxal phosphate dependent reaction. Me-THF is demethylated to THF in the methionine synthase reaction. Methionine can be activated to S-adenosylmethionine by methionine adenosyltransferase (MAT I/III or MAT II). Many methyltransferase reactions utilize S-adenosylmethionine, generating S-adenosylhomocysteine, which is hydrolyzed to homocysteine by S-adenosylhomocysteine hydrolase (SAHH). The S-adenosylmethionine dependent methylations are important in the production of phospholipids, myelin, creatine, and

many other reactions. Methylene tetrahydrofolate (Methylene-THF) is reduced to Me-THF by methylenetetrahydrofolate reductase (MTHFR). **(b)** In classic homocystinuria cystathionine beta-synthase activity is severely deficient or absent, leading to elevated levels of homocysteine, methionine, S-adenosylhomocysteine, and S-adenosylmethionine and low levels of cystathionine and cysteine. **(c)** In disorders of remethylation, including severe deficiencies, or absence, of methionine synthase (MS) or methylenetetrahydrofolate reductase (MTHFR) activities, there are elevated levels of homocysteine and S-adenosylhomocysteine, low levels of methionine and S-adenosylmethionine, and high levels of cystathionine. **(d)** In the fetus there is a severe deficiency of cystathionine gamma-lyase activity; data in this report and others support that this results in high levels of cystathionine in the presence of elevated maternal homocysteine

thrombophilia and some commercially available metabolite panels include cystathionine in combination with homocysteine. The reported case shows how a previously undiag-

nosed patient with CBS deficiency might be thought to have a remethylation defect and counseled and treated inappropriately.

Methods

Patients

Both patients were seen at the Inherited Metabolic Diseases Clinic at the Children's Hospital Colorado on a sporadic basis but were also followed by obstetricians and other physicians in their communities. The two subjects provided written informed consent for themselves and their children to participate in this retrospective chart review through a University of Colorado (COMIRB) IRB approved protocol.

Metabolite Studies

tHcy, cystathionine, methionine, total cysteine, *N,N*-dimethylglycine, and *N*-methylglycine were assayed in serum by capillary stable isotope dilution gas chromatography/mass spectrometry as previously described (Stabler et al. 1988, 1993; Allen et al. 1993). S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) were assayed in serum by stable isotope dilution liquid chromatography/mass spectrometry (Stabler and Allen 2004). The homocysteine value obtained on patient 2's baby at a later date was done in a commercial laboratory.

Results

Case Reports

Patient 1

Patient 1 was 32 years old and pregnant with a gestational age of 23 weeks when referred to the metabolic clinic for evaluation of hyperhomocysteinemia. She had been referred to Genetics during pregnancy due to a clinical diagnosis of Marfan Syndrome. A homocysteine level was ordered as classical homocystinuria is a phenocopy of Marfan Syndrome. She had been given the diagnosis of Marfan syndrome as she had been found to have upward dislocating ectopia lentis when she was 18 with high myopia. At age 25 she developed a seizure disorder controlled by medication and at age 26 she developed phlebitis following a transatlantic flight and was placed on warfarin anticoagulation. She had a history of mild developmental delay but had been in a normal classroom setting and graduated from high school. Physical exam revealed scoliosis. The biochemical data shown in Table 1 revealed severely elevated tHcy and methionine and low total cysteine. The markedly elevated cystathionine initially suggested a remethylation disorder until it was revealed by the clinic that the patient was pregnant, and had a history consistent with CBS deficiency. She was treated with B₆, methionine

restriction, B12, increased folate, betaine and cysteine supplements. Her tHcy and methionine decreased, total cysteine increased, and *N,N*-dimethylglycine and *N*-methylglycine increased documenting her compliance with betaine treatment (Stabler et al. 2013). Cystathionine fluctuated but was essentially the same at 24 and 32 weeks of pregnancy. Post delivery the cystathionine decreased to the lower end of the normal range and methionine increased markedly. CBS deficiency was confirmed by enzyme analysis.

Patient 2

The laboratory data of another patient with CBS deficiency was reviewed as she had cystathionine values measured throughout pregnancy. Case 2 was 23 years of age at the time of her pregnancy and had been diagnosed with classical homocystinuria the year prior when she presented with cavernous sinus thrombosis, which led to visual loss and right-sided hemiparesis. She also had a history of myopia and bilateral lens dislocation. She had been treated with warfarin anticoagulation since her thrombosis and was treated with vitamin B₆, folic acid, B12 injections, betaine and methionine restriction, although compliance was poor. Additional data was also available 8 years later during a fourth pregnancy, when she was treated with low molecular weight heparin anticoagulation alone. The biochemical data for the two pregnancies are shown in Table 1. In the first pregnancy, the first trimester serum values showed a low-normal cystathionine, mildly elevated methionine, and low *N,N*-dimethylglycine despite presumed betaine treatment. The cystathionine rose markedly in the second trimester and remained high at the time of delivery but fell to a value at the lower level of normal after delivery. In her fourth pregnancy at age 30 values were available at 31 weeks and at delivery, and these again demonstrated a marked elevation of cystathionine. The baby's cord blood sample revealed severely elevated homocysteine, a massive elevation of cystathionine (tenfold greater than maternal serum), elevated methionine, and low total cysteine. In addition, serum was assayed for S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) values, both of which were elevated in mother and baby. A repeat homocysteine in the child, age 2 months, was normal at 8.4 uM.

Metabolite Ratios

We have previously reported that the ratio of tHcy to cystathionine had a median of 2.8 in 118 patients with CBS deficiency as compared to 0.1 for 132 patients with remethylation defects (Stabler et al. 2013). The values in the two case patients while not pregnant were 2.46, 3.4, 3.6, and 5.5 but fell to between 0.1 and 0.19 in patient 1 and

Table 1 Clinical and biochemical data on two patients with cystathionine β -synthase deficiency

	Gestation ^a (week)	tHcys (μ M)	Cystat (nM)	Meth (μ M)	tCyst (μ M)	DMG (μ M)	MG (μ M)	SAM (nM)	SAH (nM)	Treatment
Patient 1	23	181	983	315	83	2.1	5.3			None except AC ^b
	24	124	691	64	96	1.9	4.3			
	25	83	423	165	128	34.1	14.5			
										B6, methionine restriction, betaine and cysteine
	26	71	479	152	136	76.8	20.1			“ ”
	32	67	639	158	207	225.1	28.6			“ ”
	Post	50	81	1,283	222	234	86.5			“ ”
Patient 2	Post	123	50	1,560	178	109.2	29.5			“ ”
	Pre	310	85							AC ^b
	First Tri	136	85	55	108	3	6.1			B6, folic acid, B12, betaine and methionine restriction (unknown compliance)
	Second Tri	182	1,432							
	Delivery	134	2,942	279	99					
	Post	232	42	118	89	5.3	15.7			Only LMWH ^c
Fourth pregnancy	31	232	4,354							
Mother	Delivery	166	3,115	73	98	2.6	7	266	382	
	Cord blood	169	30,443	119	111	4.1	8.6	840	366	
	2 months	8.4								
Normal ranges		(5.1–13.9)	(44–342)	(13–45)	(200–361)	(1.4–5.3)	(0.6–2.7)	(71–168)	(8–26)	

^a Gestation is noted in weeks or as to trimester, at time of delivery or pre- or post-pregnancy state^b AC is anticoagulant therapy^c LMWH is low molecular weight heparin injections

0.045 and 1.6 in patient 2, completely overlapping the values previously seen for remethylation disorders. The ratio of methionine to cystathionine is also useful in distinguishing CBS deficiency from remethylation defects since it is quite elevated in the former (Stabler et al. 2013; Bártl et al. 2014). The methionine to cystathionine ratios were much lower in the 2 patients while pregnant ranging from 23 to 647 as compared to the non-pregnant values of 2,809 to 31,200 but were always higher than that reported for remethylation defects (Bártl et al. 2014).

Discussion

Both patients with CBS deficiency delivered healthy babies, although the tHcy was not controlled for most of patient 1's gestation nor for both gestations of patient 2. Patient 1 demonstrated the massive elevations in *N,N*-dimethylglycine seen with adequate betaine treatment, but

patient 2 had normal range *N,N*-dimethylglycine suggesting low or no intake of betaine (Allen et al. 1993). The high cystathionine values with a low tHcy to cystathionine ratio were initially unexpected, as the ratio of tHcy to cystathionine is considered to be a robust way to diagnose probable CBS deficiency since remethylation disorders, both due to inborn errors and to severe vitamin B12 or folate deficiency, show a much lower ratio of these compounds (Stabler et al. 2013). The cord blood for patient 2's baby was very abnormal with severe hyperhomocysteinemia, massive cystathioninemia with a tenfold elevation compared to maternal serum, and a 100-fold elevation compared with normal values. There were also large elevations in SAM and in particular, SAH, which was 10 times normal. The normal tHcy later in infancy showed that the baby did not have homocystinuria. Thus, the values in the cord blood must reflect in utero hypermethioninemia and hyperhomocysteinemia due to the elevated values of these in the mother. Cystathionine is converted to cysteine by

cystathionine gamma-lyase, an enzyme that is deficient in fetal life, which increases post-natally in the first weeks of life (Gaull et al. 1972). A likely explanation for the hypercystathioninemia in the two women reported here and in the infant, are that the fetus with presumed 50% of normal CBS activity, converted elevated homocysteine derived from the mother to cystathionine and returned it to the mother's circulation since the fetus could not metabolize cystathionine (Fig. 1d). This is the first report of a massive elevation of cord blood cystathionine in maternal CBS deficiency.

The fact that cystathionine can be markedly elevated during pregnancy in women with CBS deficiency is important to know in order to prevent errors in diagnosis and might also be monitored in pregnancy in order to assess efficacy of therapy. Women with CBS deficiency are at increased risk for thrombosis during pregnancy and the literature documents CBS patients diagnosed, as was our patient, in the peripartum period (Kurczynski et al. 1980; Constantine and Green 1987; Yap et al. 2001; Levy et al. 2002; Pierre et al. 2006). Patients without severe connective tissue complications may present in adulthood (Maclean et al. 2002; Magner et al. 2011). In addition some patients are confused with Marfan Syndrome as was patient 1 (Berry and Levy 2010). THcy values are frequently determined as part of a hypercoagulable screen in adult medicine. A panel measuring serum/plasma tHcy, cystathionine, and methylmalonic acid is widely available from commercial laboratories in the USA and the results could lead to the erroneous conclusion that a patient had a remethylation defect such as severe methylenetetrahydrofolate reductase deficiency as the cause of elevated tHcy and cystathionine. The necessity to also measure serum methionine which may be low in remethylation defects and elevated in CBS deficiency may not be recognized by hematologists or obstetricians who are not familiar with inborn errors of metabolism.

While there are many reports of successful pregnancy with delivery of healthy infants in patients affected by CBS deficiency (Levy et al. 2002; Pierre et al. 2006), increased fetal loss and malformations have also been reported (Constantine and Green 1987). The severe hyperhomocysteinemia in the baby's cord blood and marked abnormalities of SAM and SAH could contribute to fetal anomalies. SAH is an inhibitor of most transmethylation reactions, and it is not known whether this massive increase in SAH throughout gestation would be detrimental. Elevated homocysteine could also impair uptake of other amino acids by the placenta (Regnault et al. 2007). The time course of the accumulation of these metabolites can be estimated by viewing the results of patient 2 in the first pregnancy, the

first and second trimester, and time of delivery. Cystathionine and methionine were normal in the first trimester but by the second trimester cystathionine had increased more than tenfold suggesting that the fetus had already developed hyperhomocysteinemia and hypermethioninemia. The lower cystathionine and homocysteine values in patient 1 as compared to patient 2 likely reflect the effect of betaine treatment as suggested by elevated *N,N*-dimethylglycine in patient 1 and not patient 2 as well as better compliance with dietary restriction of methionine. This would lower the homocysteine exposure of the fetus.

There are only a few previous reports of total homocysteine or the disulfide, homocystine, and methionine values in amniotic fluid, fetal tissues, or cord blood in the fetuses of mothers with CBS deficiency. In one case report, amniotic fluid at about 16 weeks gestation showed severely elevated methionine, 590 $\mu\text{mol/L}$, (control fluid: 20 $\mu\text{mol/L}$) elevated homocystine, 20 $\mu\text{mol/L}$ (control fluid: not detected), and no detectable cystathionine. The affected mother had an elevated plasma methionine of 400 $\mu\text{mol/L}$ and a homocystine of 40 $\mu\text{mol/L}$; total homocysteine was not reported. The fetus was aborted at 20 weeks and had massively increased liver and brain cystathionine as well as elevated methionine (Rassin et al. 1979). Another case report identified a similar elevation of methionine in amniotic fluid at 18 weeks gestation of 590 $\mu\text{mol/L}$ (Kurczynski et al. 1980). It appears from this limited data that the fetus of an affected mother is exposed to high concentrations of methionine and homocysteine, starting from the second trimester at least. Levy et al. (2002) reported that total homocysteine, 155 $\mu\text{mol/L}$, and methionine 117 $\mu\text{mol/L}$ were elevated in umbilical cord plasma when a mother with homocystinuria had elevated homocysteine at delivery. Cystathionine was not measured.

We have previously reported that serum cystathionine rose massively in a patient with moderately severe methionine adenosyl-transferase (MAT I/III) deficiency during several pregnancies (Mudd et al. 2003). We proposed that the elevated methionine in the mother was delivered to the fetus who produced cystathionine but since the fetus lacked cystathionine gamma-lyase, the cystathionine was returned to the mother's circulation. The present cases further support this mechanism of maternal cystathionine elevation in pregnancy in both disorders.

It is unclear if elevated cystathionine is harmful to the fetus; however, in post-natal life cystathionine gamma-lyase deficiency (cystathioninuria) is a benign disorder (Kraus et al. 2009). In addition, a report of maternal cystathionine gamma-lyase deficiency showed massive increases of cystathionine in amniotic fluid in 2 pregnancies of 45 and 54 $\mu\text{mol/L}$ as compared to normal (expected $<1 \mu\text{mol/L}$) as reported for their laboratory. The infants had cord blood

values that were also massively elevated at 12 and 16 $\mu\text{mol/L}$ (Vargas et al. 1999), which are lower than that of the infant of patient 2, at 30 $\mu\text{mol/L}$ (30,443 nmol/L).

Conclusions

We have assayed methionine-related metabolites in two patients with CBS deficiency during pregnancy and demonstrate that cystathionine values are increased above the pre- and post-pregnancy values by 10- to 20-fold during gestation. The cystathionine value in the cord blood of the one infant evaluated was tenfold elevated above the concurrent maternal serum value. Recognition that cystathionine is elevated during pregnancy will prevent diagnostic errors in pregnant CBS patients who may have not been previously diagnosed with classical homocystinuria prior to their pregnancy. Maximum biochemical control should be encouraged in order to limit exposure of the fetus to the lowest concentrations of homocysteine and methionine possible.

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Take Home Message

Cystathionine is low in patients with cystathionine beta-synthase deficiency except during pregnancy when fetal exposure to high homocysteine results in fetal synthesis of cystathionine and transfer to the mother's circulation, which may confound the specific diagnosis of hyperhomocysteinemia.

Contributions of Authors

Sally Stabler, Janet Thomas, and Renata Gallagher were responsible for planning the details in the manuscript. Sally Stabler and Robert Allen were involved in the conduct of the laboratory measures in the manuscript. Janet Thomas, Cynthia Freehauf, and Renata Gallagher were involved in the conduct of obtaining the clinical measures. Sally Stabler and Renata Gallagher wrote the bulk of the manuscript with contributions from the other authors.

Guarantor for Chapter

Sally P Stabler serves as the guarantor for this chapter, accepting full responsibility for the work. She had access to all the data and controlled the decision to publish.

Conflict of Interest

Sally Stabler and Robert Allen and the University of Colorado have competing interests because a company has been formed at the University of Colorado to assay homocysteine, methylmalonic acid, and cystathionine. Cynthia Freehauf, Janet Thomas, and Renata Gallagher declare that they have no conflict of interest.

Funding for Research

There was no funding for the research.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent was obtained from all patients and their children for being included in the study.

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