

Case Report: Heavy Metal Burden Presenting as Bartter Syndrome

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Abstract

CONTEXT: Maternal transfer of heavy metals during fetal development or lactation possibly contributed to the clinical manifestations of Bartter syndrome and developmental delay in the offspring. **CASE PRESENTATION:** An 11-month-old child diagnosed with Bartter syndrome and failure to thrive was treated concurrently for elevated metal burden while he was undergoing standard medical interventions. Treatment with body-weight doses of meso-2,3-dimercaptosuccinic acid (DMSA) reduced the body burden of lead, beryllium, copper, mercury, and cadmium at the three- and sixth-month follow-up tests. During the course of the six-month treatment, the patient gained 2.4 kg (5.2 lb) and grew approximately 9.5 cm (3.75 in). His weight shifted from significantly below the 5th percentile in weight to within the 5th percentile, and from below the 5th to within the 10th percentile for length. **DISCUSSION:** The child's acquisition of lead, beryllium, and copper correspond to his mother's history of stained glass assembly and occurred during fetal development or lactation, since there were no other identifiable sources that could have contributed to the heavy metal burden. Tests for known genetic mutations leading to Bartter syndrome were all negative. **RELEVANCE TO CLINICAL PRACTICE:** This case report highlights the potential benefit of DMSA for treatment of heavy metal body burden in infants who present with Bartter syndrome. (*Altern Med Rev* 2010;15(4):303-310)

Introduction

Bartter syndrome is a genetic disorder that is comprised of various genetic mutations that lead to a renal electrolyte imbalance. First described in 1962, Bartter syndrome consists of four forms characterized by hypokalemic metabolic alkalosis, hyperaldosteronism, and juxtaglomerular apparatus hyperplasia in the presence of normal blood pressure,¹ and includes an array of molecular and genetic influences that impair sodium chloride transport in the renal system.² Bartter syndrome

type 1 is associated with the gene SLC12A1 encoding a sodium-potassium-chloride cotransporter (NKCC2) expressed in the thick ascending limb of the loop of Henle. A mutation of this gene will cause a defect of the sodium-potassium-chloride exchange protein in the ascending loop of Henle.³ Bartter syndrome type 2 is described as a mutation in the potassium channel gene ROMK, also known as KCNJ1. This gene is believed to be a regulator of cotransporter activity and is an ATP-sensitive potassium channel that reprocesses reabsorbed potassium back to the tubule lumen. Bartter syndrome type 3 (classic form) is caused by a mutation in the kidney chloride channel B gene (CLCNKB) or with a simultaneous mutation in the CLCNKA gene. Infantile Bartter syndrome with sensorineural deafness, or type 4, is caused by a mutation in the Barttin (BSND) gene.^{2,4-6} Several genes have been associated with the different phenotypic varieties of Bartter syndrome.⁴⁻⁶ The neonatal and infantile form of Bartter syndrome is rare and includes these additional features: polyhydramnios, premature delivery, growth retardation, hypercalciuria, nephrocalcinosis,^{7,8} and systemic overproduction of prostaglandins – hyperprostaglandin E syndrome (HPE).^{9,10}

This case report describes an 11-month-old male infant clinically diagnosed with Bartter syndrome who tested positive for elevated fecal levels of lead, beryllium, and copper, along with detectable levels of mercury and cadmium. He responded well to oral chelation with meso-2,3-dimercaptosuccinic acid (DMSA). His Bartter syndrome presentation, characterized by failure to thrive, dehydration, hypokalemia, alkalosis, and a very high urinary excretion of prostaglandin E2, improved significantly as his heavy metal levels declined.

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Case Presentation

The patient, a Caucasian male, was born at 40 weeks gestation to non-consanguineous parents. He was the first child of a 28-year-old woman (G1P1) and a 33-year-old man. The pregnancy was uncomplicated, routine prenatal visits were unremarkable, and ultrasound performed at 22 weeks gestation revealed no abnormalities. The child was birthed naturally at home by a midwife without complications. His birth weight (3.97 kg; 8 lb, 12 oz), length (54 cm; 21.25 in), and head circumference were all within the 75th percentile (Table 1).

At the first week follow-up, the patient's weight was the same as his birth weight. All reflexes were normal and physical examination revealed a healthy baby. He was being breast fed and demonstrated proper latch technique. At this visit both his weight and length decreased from the 75th to the 25th percentiles. Although the patient did not gain weight at the first month follow-up, the child's pediatrician was not alarmed because no abnormalities were detected and the child was exclusively breast fed.

At the three-month follow-up, there was little improvement in growth and weight gain. On exam, the patient was agitated and feeding poorly. The child's pediatrician introduced formula feeding in conjunction with breast feeding to encourage weight gain. The serum potassium levels were within reference range (although the specimen was hemolyzed, making accuracy questionable).

At age 4.5 months, the child was admitted to the local Children's Hospital to evaluate for developmental delay and failure to thrive. His weight on admission was 4.5 kg (9.8 pounds), placing him below the 5th percentile (-4.2 standard deviations below the mean); his length was 59.5 cm, which was below the 5th percentile for his age (-2.9 standard deviations below the mean); and his head circumference measured 40.5 cm (below the 5th percentile and -2.1 standard deviations below the mean). He was diagnosed with Bartter syndrome after a nonhemolyzed sample of blood revealed a critically low serum potassium level and evidence of hypercalciuria, with urine calcium:creatinine ratios in the 3.5 to 4.1 range. The initial electrolyte abnormalities included sodium 124

(normal: 133-145 mmol/L), potassium 2.2 (normal: 3.6-5.2 mmol/L), chloride 78 (normal: 98-108 mmol/L), and bicarbonate 40 (normal 17-27 mmol/L). An ultrasound of the kidneys showed no calcifications, and a sweat chloride test was negative. An auditory brainstem response evaluation revealed normal auditory thresholds in the 500-8,000 Hz range bilaterally. Synchrony of the auditory system throughout the brainstem was normal.

The child was initially treated with IV fluids and normal saline with 40 mEq of potassium chloride per liter. He remained in the hospital for 11 days and was monitored closely. Daily weight improvements of about 0.08-0.175 kg were recorded, and at discharge he weighed 5.13 kg (11.3 lb). He was discharged on a daily regimen of 32 ounces of formula mixed with 1 teaspoon of Celtic sea salt and 10 mL potassium chloride, 2.5 mg indomethacin, and 5 mg spironolactone (the latter twice daily).

At nine months, the patient's weight was 6.7 kg (14.8 lb) and length was 66.7 cm (26.25 in), both below the 5th percentile. His head circumference was 44 cm, which placed him between the 10th and

Key words: Bartter syndrome, heavy metal, toxic metal, DMSA, mercury, lead, beryllium, copper, cadmium, developmental delay, failure to thrive

Table 1. Growth Measurements from Birth to 18 Months

| Age | Weight (kg) | Length (cm) | Head Circumference (cm) |
|------------|-------------|-------------|-------------------------|
| Birth | 3.97 | 54 | <75th percentile |
| 1 week | 3.97 | 54 | NA |
| 1 month | 3.97 | 54 | NA |
| 3 months | 4.5 | NA | NA |
| 4.5 months | 4.5 | 59.5 | 40.5 |
| 9 months | 6.7 | 66.7 | 44 |
| 11 months | 6.8 | 67.9 | NA |
| 12 months | 7.3 | 68.6 | 44.5 |
| 13 months | 8.1 | NA | NA |
| 14 months | 8.6 | 71.1 | NA |
| 17 months | 9.2 | 77.5 | 47 |

25th percentile. He was responding to his own name, understanding and speaking a few words without meaning, and able to roll on his side. The patient attended routine follow-up visits with the nephrologist and registered dietician. At least twice a month his parents needed to take him to the emergency department for a variety of conditions, including dehydration, recurrent emesis, constipation, and seizures. His medications at this point included 2 tablespoons of sodium chloride per 32 ounces of formula, 80 mL potassium chloride daily, 5 mg indomethacin twice daily, 10 mg spironolactone twice daily, 1 mg amiloride daily, and 1 g magnesium daily, which were administered through a nasogastric tube.

At age 11 months, the child was referred to the Southwest Naturopathic Medical Center (SNMC) for additional evaluation. The child weighed 6.8 kg (15 lb) and measured 67.9 cm (26.75 in) at evaluation. History from both parents revealed significant environmental toxin exposure. Both the mother and father lived for over three years in Hawaii, with known exposures to volcanic fog (commonly referred to as “VOG” and high in elemental mercury), and in a house built before 1978 that presumably contained lead paint. Both had high consumption of fish (3-4 times per week) during their lifetimes and the mother continued to consume moderate amounts (2-3 times per week) during the first trimester of pregnancy. Importantly, the mother worked for 14 years with lead solder in her family’s stained glass business. An amalgam of beryllium-copper alloy is often mixed with lead and mercury for stained glass construction.

Two fecal samples from the patient were

collected on different days and sent to Doctor’s Data, Inc. (DDI) laboratory (St. Charles, IL) for heavy metal analysis. The level of lead was 1.68 mg/kg (reference range <0.50), beryllium 0.036 mg/kg (reference range <0.009), and copper 100 mg/kg (reference range <60) (Table 2). Heavy metals present in the sample, but not above the lab’s normal reference ranges, included mercury at 0.017 mg/kg (reference range <0.05) and cadmium at 0.08 mg/kg (reference range <0.50). The laboratory reference ranges placed lead and beryllium above the 95th percentile and copper near the 90th percentile. The values for mercury and cadmium were below the 68th percentile. It should be noted that the fecal test is expected to reflect current exposures, but not necessarily total tissue burden.

Because this patient’s primary source of heavy metal burden was apparently from maternal transference during fetal development, lactation, and/or from pre-conception, both parents were checked and found to have high levels of these compounds. The mother was administered 1,750 mg DMSA (based on a 30 mg/kg body-weight dose), followed by a six-hour urine collection, which revealed levels of lead at 11 µg/g creatinine (reference range <5 µg/g creatinine), mercury at 7.8 µg/g creatinine (reference range <4 µg/g creatinine), and cadmium at 0.9 µg/g creatinine (reference range <2 µg/g creatinine). The father was administered 2,250 mg of DMSA, followed by a six-hour urine collection, which revealed levels of lead at 13 µg/g creatinine, mercury at 5 µg/g creatinine, and cadmium at 0.4 µg/g creatinine. Beryllium and copper were not evaluated on the parents’ urine tests.

Table 2. Fecal Heavy Metal Measurements (mg/kg)

| Metal | Reference Range | Baseline at Age 11 Months | 3 Month Follow-up at Age 14 Months | 6 Month Follow-up at Age 17 Months |
|-----------|-----------------|---------------------------|------------------------------------|------------------------------------|
| Beryllium | <0.009 | 0.036 | 0.008 | 0.005 |
| Cadmium | <0.5 | 0.08 | 0.15 | 0.32 |
| Copper | <60 | 100 | 53 | 49 |
| Lead | <0.50 | 1.68 | 0.21 | 0.45 |
| Mercury | <0.05 | 0.017 | 0 | 0 |

The child was continued on all medications as directed by his nephrologist with the addition of a total daily dose of 200 mg DMSA in three divided doses for two days a week (Monday and Thursday), with mineral support (a children's liquid multi-vitamin) and additional magnesium on the days in between. During the first three months of treatment (age 11-14 months), DMSA was administered via a nasogastric feeding tube along with his other medications. As he improved and the need for his feedings and medications via the nasogastric tube ceased, the DMSA was flavored or mixed with food (such as applesauce and puréed vegetables).

After one month on this protocol, the patient's weight increased by 1.27 kg (2.8 lb) to a total of 8.1 kg (17.8 lb), compared with prior month gains of 0.05 kg/month from ages 9-11 months (Table 1). Other signs of improvement included an ability to walk with the help of his parents and vocabulary increase from a few words to at least 10 words with meaning. He also became more expressive and was able to communicate with words and gestures. He began sleeping through the night and had no vomiting. He had an increased appetite and was feeding well – eating three meals a day for half an hour to an hour at each meal. He showed interest in solid foods and his parents were able to transfer him from formula to a combination liquid/solid food diet. There were no emergency hospital visits between the initial intake at SNMC and the follow-up visit – the longest duration he had experienced without an emergency hospital visit. Although he had tended to have constipation, he began to exhibit increasingly loose stools and diarrhea, which was corrected by lowering the dose of magnesium. In addition, with consultation from the nephrologist, he was able to decrease the dosage of potassium chloride and sodium chloride.

Another fecal heavy metal test was conducted at his three-month follow-up visit (age 14 months). The lead level had dropped to 0.21 mg/kg, mercury dropped to a nondetectable range, beryllium dropped to 0.008 mg/kg, and copper dropped to 53 mg/kg, but cadmium excretion increased to 0.15 mg/kg. All values were below the 68th percentile. The patient now weighed 8.6 kg (18.9 lb) and his length was 71.1 cm (27.7 in), which was a 3.2-cm increase since the initial evaluation. He continued to sleep throughout the night, was eating three to four meals a day without complications, having no vomiting, actively crawling and walking without assistance, and continuing to use more words and combine words with meaning. Based on laboratory evaluation, his nephrologist determined he no

longer needed to consume sodium chloride or potassium chloride during his feedings.

At the six-month follow-up visit (age 17 months), the patient's weight and length had increased by 35- and 14 percent, respectively, compared to the initial visit. He weighed 9.2 kg (20.2 lb), was 77.5 cm (28 in) in length, and had a head circumference of 47 cm (18.3 in). His weight placed him slightly below the 5th percentile, length in the 5th percentile, and head circumference in the 25th percentile. His third fecal heavy metal test, conducted after six months of treatment, revealed lead at 0.45 mg/kg, beryllium at 0.005 mg/kg, copper at 49 mg/kg, cadmium at 0.32 mg/kg, and mercury below detection levels. In addition to persistence of all previous improvements, he was able to walk a few steps and stand independently, his vocabulary had increased to more than 20 words, and he continued to show improvement in communication with gestures and meaningful words.

A genetic analysis completed by the Center for Nephrology and Metabolic Disorders Laboratory for Molecular Diagnostics (Weisswasser, Germany) found no mutation for Bartter syndrome by direct sequencing. This included the *SLC12A1* and *KCNJ1* genes consistent with the patient's clinical presentation and other known genes associated with Bartter syndrome (*CLCNKB*, *CLCNKA*, and *BSND*).

Discussion

This study supports the hypothesis of maternal transfer of heavy metals that appear to have contributed to the clinical manifestations of Bartter syndrome and developmental delay. Failure to find one of the mutations known to cause Bartter syndrome appears to indicate that either this genetic disease entity was not the cause of his Bartter-like presentation or that there are other currently unknown genes involved in Bartter syndrome.

In this case presentation, the child acquired a heavy metal burden during fetal development and/or lactation. The patient's initial fecal metals test revealed elevated lead, beryllium, and copper that corresponded to the mother's history of stained glass assembly and other environmental exposures. There are no other identifiable sources of heavy metals because the patient was solely breast fed until age four months, at which point he was introduced to formula to encourage weight gain. Solid foods were not introduced to the child until about three months after the treatment protocol with DMSA was begun.

Gulson et al demonstrated through longitudinal lead isotope studies that maternal bone lead can readily pass to the fetus *in utero*.¹¹ The half-life of bone lead is estimated to be 10-25 years,^{12,13} and maternal bone lead stores can predict adverse outcomes better than blood lead levels.¹⁴ Lead is mobilized from bones into the bloodstream during pregnancy due to the fetal demands for calcium, resulting in bone resorption.¹⁵ The placenta does not offer a barrier to lead or beryllium as they can pass through the umbilical cord to the fetus.^{16,17} During lactation, due to the need to maintain adequate calcium levels, lead continues to be mobilized from maternal bone stores, providing undesired continuous transfer from breast milk.¹¹ Beryllium, a divalent cation like lead, is also stored in the bones and may also be liberated during calcium metabolism.¹⁸

Breast feeding provides many benefits to infant development and continues to be highly recommended over the use of infant formulas. Maternal lead burden and its outcomes¹⁹ have been described to cause low birth weight,²⁰ slow growth,²¹ and poor mental development.²² If breast milk with its excellent balance of nutrients is unavailable, nutrient imbalance can occur with possible adverse health effects.²³ Breast milk is the major source of fat, calories, and calcium for the child. Calcium supplementation itself has been shown to decrease the mobilization and absorption of lead,²⁴ while higher levels of dietary fat and calories have been attributed to increased absorption of lead in children.²⁵

Although the effects of lead, mercury, and cadmium on renal impairment have been documented extensively in the literature,²⁶⁻³¹ the effects of beryllium and copper on the renal system are not as evident. Studies have shown that lead at low levels can progressively impair renal function and accelerate tubulointerstitial injury in chronic kidney disease.³² Waalkes et al describe a study of lead exposure in mice during gestation and lactation that resulted in tumors and atypical hyperplasia of renal tubular cells.³³ It is interesting to note that the first description of a new syndrome of hyperplasia of the juxtaglomerular complex observed in 1962, later named Bartter syndrome for the author who first described it, emerged roughly two decades after leaded gasoline use began to increase in the late 1940s.

Fecal samples to assess heavy metals were used for ease of collection from an infant. Measurements in fecal samples are possible because biliary excretion of lead, mercury, and

cadmium is the primary route of elimination from the body. Beryllium and copper are also secreted by the liver into the bile for excretion in the feces, with only a small amount of copper excreted in the urine via the kidneys. Fecal testing results were not provoked with the treatment agent because DMSA does not increase mobilization of heavy metals through the feces.^{34,35} The initial levels of lead and beryllium were significantly elevated beyond the 95th percentile and copper near the 90th percentile according to DDI reference ranges. Levels of cadmium and mercury in the patient's fecal samples were not significantly elevated according to the DDI reference ranges, but are noted because of their known effects on renal impairment. In fact, mercury is one of the heavy metals that has been associated with potassium-wasting nephropathy.³⁶ Currently, there is no commonly accepted national standard for fecal heavy metal levels for comparison. The CDC Fourth National Report on Human Exposure to Environmental Chemicals³⁷ provides information on blood and urine samples for selected chemicals and heavy metals, but not reference ranges for fecal heavy metals.

All the metals detected in this patient have been implicated in the literature to alter gene expression.^{5,38-42} Antenatal Bartter syndrome is strongly associated with certain gene mutations, but biochemical heterogeneity exists between the different forms. For instance, in some patients with Bartter syndrome, the SLC12A3 gene on chromosome 16 can influence the Na-K-2Cl cotransporter of the distal convoluted tubule; while the CLCNKB genes alter the thick ascending loop of Henle in other patients with Bartter syndrome.^{5,40} Although the role of heavy metals in this process remains undefined, the possibility of certain heavy metals causing a phenotypic response that mimics the genotypic cause of Bartter's remains possible. Beryllium, lead, and mercury have been described to inhibit the repair of damaged DNA, and as a consequence result in somatic and germline mutations.^{38,39,41,42} Treatment with DMSA provided this child with a reduction in heavy metal body burden, resulting in lower values of the metals on follow-up testing. DMSA first binds to metals for which it has a strong affinity or to lesser-affinity metals that are in abundance. DMSA often mobilizes lead first, then mercury. When levels of these metals are diminished, other metals, such as cadmium, are observed to be excreted at higher levels on subsequent tests.^{43,44} The authors observed a rise in fecal cadmium on the third test performed on this patient. Although

the value of lead was also slightly higher on the third test, the value was substantially lower relative to baseline testing, indicating a significantly lowered heavy metal body burden. Mercury became nondetectable and beryllium and copper decreased significantly on both follow-up tests. As the heavy metal body burden diminished, clinical improvements and increased weight and growth were observed.

Chelation therapy with DMSA has been documented in the literature to safely lower circulating levels of lead in the pediatric population when given in body-weight doses.⁴⁵ The use of DMSA for mercury overload in children has also been shown to be safe and effective at a body-weight dose of 30 mg/kg.⁴⁶ Due to lack of studies on improvement in cognition and behavior in some pediatric populations, the American Academy of Pediatrics does not recommend chelation for blood levels less than 25 µg/dL.⁴⁷ They suggest no evidence exists that chelation avoids or reverses neurotoxicity, while failing to acknowledge potential benefits in other aspects of health.

The clearance of lead from the blood occurs as lead moves into bone and other target tissues. Lead that is not stored into bone or target tissue is eliminated from the body through urine and stool.⁴⁸ Bone lead can re-equilibrate into the circulation due to trauma (broken bones), osteoporosis,⁴⁹ endocrine dysfunction,⁵⁰ chemotherapy,⁵¹ lack of physical activity,⁵² and pregnancy.⁵³ As a result, bone stores of lead acquired through maternal circulating lead levels during fetal development and lactation can potentially be a source of endogenous lead exposure in the child later in life and into adulthood. While the maternal bone turnover during lactation can be greater than during fetal development⁵⁴ and result in increased liberation of lead from bone stores, breastfeeding continues to be highly recommended because it provides many benefits and infant formula has been found to be contaminated with lead.^{55,56} A vicious cycle of endogenous lead exposure can continue to pose a threat to future generations, even though exogenous sources of lead exposure have diminished over the years.⁵⁴

Conclusion

DMSA was used in an 11-month-old child, previously diagnosed with Bartter syndrome, who showed elevated fecal heavy metal levels. As the DMSA reduced the total body burden of heavy metals, the child began to regain his health. Not

only did his weight and growth improve, his developmental milestones were restored and his need for medication was greatly diminished. It is far from clear as to whether this was heavy metal burden masquerading as Bartter syndrome or if the heavy metals merely exacerbated a genetic predisposition to altered kidney function. While we have no way of knowing how many children who are diagnosed with Bartter syndrome have a heavy metal burden, the testing for this is of minimal cost and is noninvasive. Performing such testing may reveal other children who could also benefit from this therapy. In addition, preconception screening for heavy metals and specialized nutrition to prevent transfer of heavy metals during pregnancy and lactation could be beneficial.

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Competing Financial Interests Declaration

Dr. Crinnion has consulted for Metamatrix Clinical Laboratory, which offers heavy metal testing to their clients. Metamatrix was not used for this case study and provided no support to this case or its publication. Dr. Tran consults for Doctors Data, Inc., which was used for laboratory testing. The laboratory provided no support to this case or its publication. This case report was completed prior to Dr. Tran serving as a consultant.

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