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Is Serum Methylmalonic Acid a Reliable Biomarker of Vitamin B12 Status in Children with Short Bowel Syndrome: A Case Series

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Abstract

We describe 3 patients with short bowel syndrome (SBS) who had persistently elevated serum methylmalonic acid (MMA) levels while being treated for vitamin B12 deficiency. Following treatment for presumed small bowel bacterial overgrowth, MMA levels normalized. Among patients with SBS, MMA levels may have limited specificity for vitamin B12 deficiency.

Key Indexing Terms

Short Bowel Syndrome (SBS); Vitamin B12 deficiency; Methylmalonic acid (MMA); Small Bowel Bacterial Overgrowth (SBBO)

Short bowel syndrome (SBS) results from a reduction in bowel surface area leading to inadequate nutrient and fluid bowel absorption[1]. The wide variety of underlying etiologies of SBS and unique anatomic features impact short and long-term outcomes.[1, 2] Multiple micronutrient deficiencies, including vitamin B12 deficiency, have been described among patients with SBS, particularly after transition from parenteral to full enteral nutrition[3–5]. A variety of factors including terminal ileal resection and gastric acid blockade, can significantly elevate the risk of vitamin B12 deficiency[6, 7]. Clinical manifestations of vitamin B12 deficiency include megaloblastic anemia, bone marrow failure, demyelinating diseases, thrombosis, and psychiatric symptoms[6]. Early assessment of vitamin B12 status and evaluation of response to supplementation is important, given the potential to reverse

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symptoms of vitamin B12 deficiency with prompt treatment. Vitamin B12 deficiency has been commonly defined as a serum level of <200 pg/mL, however metabolites such as total homocysteine (tHcy) and methylmalonic acid (MMA) can serve as complementary markers of B12 deficiency[7]. Metabolism of tHcy and MMA occurs via vitamin B12 dependent enzymatic pathways, and thus elevations in these byproducts serve as indicators of vitamin B12 status[6, 7]. Measurements of MMA and tHcy levels decline after adequate supplementation and are often used to confirm treatment response[6–8]. Changes in MMA levels in particular have been shown to have a higher sensitivity for vitamin B12 deficiency and aid in early detection of deficiency in comparison with serum B12 levels alone [6, 8, 9].

A decline in MMA serum levels following antibiotic treatment has been observed in children with inborn errors of metabolism, such as propionic acidemia and methylmalonic acidemia[10]. These observed changes in MMA concentration were hypothesized to be secondary to changes in gut flora, which included a reduction in bacterial counts and propionate measures, as well as a shift in bacterial population. [11] A case of isolated elevation in MMA concentration was described in an adolescent with SBS and chronic small bowel bacterial overgrowth (SBBO) with known vitamin B12 deficiency. The patient was treated with metronidazole and his high MMA serum level normalized. It was hypothesized that the patient's SBBO led to an overproduction of propionate by intestinal bacteria which in turn resulted in elevated plasma MMA levels[12]. In this report, we describe 3 patients with short bowel syndrome receiving parenteral vitamin B12 supplementation that had elevated plasma MMA levels on routine monitoring, with subsequent normalization of MMA after antibiotic treatment for presumptive SBBO.

Case Reports

Case 1

A 6-year-old girl had been diagnosed with segmental volvulus, meconium cyst with perforation and meconium peritonitis as a neonate. She had undergone initial resection of her small bowel (approximately 8 cm), and her clinical course was complicated three months later with small bowel obstruction that resulted in resection of her distal ileum, ileocecal valve (ICV), and proximal colon. She was placed in intestinal continuity with an ileocolonic anastomosis. By 8 months of age she was weaned from parenteral nutrition (PN) support. At twenty-four months of age (13 months after the cessation of PN), she was noted to have vitamin B12 deficiency (serum level = 151 pg/mL) and therefore began treatment with intramuscular (IM) injections of vitamin B12 (500 μg monthly). Following treatment, she was observed to have an appropriate response with normalization of her serum B12 (>200 pg/mL) and tHcy levels (ranging from 4.7 to 7.7 μmol/L). Her serum MMA level, however, remained elevated (1.5–1.6 μmol/L; normal = <0.9 μmol/L). Although she was largely asymptomatic for SBBO (no vomiting, abdominal distension or difficulties with tolerating enteral nutrition), she was treated with a one week course of metronidazole, four years after her initial B12 deficiency diagnosis, with no changes to her monthly IM B12 supplementation. Repeat laboratory evaluation revealed a normal plasma MMA level (0.3 μmol/L).

Case 2

At 1 month of age, a premature infant (28 weeks gestation) developed necrotizing enterocolitis resulting in resection of 38 cm of necrotic distal ileum, and the ileocecal valve. He subsequently underwent an ileocolonic anastomosis and continued to required parenteral nutrition until age two years. He developed biochemical signs suggestive of vitamin B12 deficiency with elevated tHcy (11.0 μmol/L), MMA (2.0 μmol/L), with borderline low serum B12 levels (289–369pg/mL) at age three years (14 months after the cessation of PN) and was started on IM Vitamin B12 injections (500 mcg monthly). Subsequently, his serum B12 (>500 pg/mL) and homocysteine (<10 μmol/L) levels improved, but his MMA serum levels remained elevated (ranging from 1–6 μmol/L). Clinically, he was tolerating his enteral nutrition well, without overt signs of feeding intolerance or malabsorption. He was started on empiric SBBO treatment with metronidazole seven months after his initial B12 deficiency diagnosis. Following a one week course of treatment, repeat MMA serum level (<1 μmol/L) was within normal limits.

Case 3

A 2-month-old female with a history of prematurity (26 weeks gestation) developed necrotizing enterocolitis and underwent resection of 50 cm of necrotic bowel from the mid-small bowel to the ileocecal valve. She subsequently underwent a jejunocolonic anastomosis and transitioned from parenteral to full enteral nutrition. She was started on IM vitamin B12 supplementation (500 mcg monthly), due to biochemical evidence of B12 deficiency with low serum vitamin B12 (<150 pg/mL), an elevated tHcy (11 μmol/L) and an elevated MMA (2.1 μmol/L) at 1.5 years of age (9 months after the cessation of PN). Following monthly IM injections of vitamin B12, her diagnostic labs of vitamin B12 (>200pg/mL) and tHcy (<10μmol/L) levels demonstrated adequate response. Her MMA level was initially appreciated to be within normal levels (<.9 μmol/L), but after almost two years of supplementation and laboratory screening she had an elevated MMA level (2.5 μmol/L), with other biochemical makers (B12 level, tHcy, Hg) being normal. Given the isolated abnormality, she was started on metronidazole due to concern for subclinical bacterial overgrowth. After 1 week of treatment with metronidazole, her MMA level (0.2 μmol/L) returned to normal.

The Table summarizes the laboratory values of our 3 subjects, including hemoglobin, mean red cell volume, and serum levels of B12, MMA, and tHcy before and after antibiotic treatment. The repeated laboratory tests were obtained seven days after initiation of antibiotic treatment.

Discussion

We describe three children with short bowel syndrome who had undergone terminal ileal resection, with confirmed B12 deficiency receiving intramuscular B12 with established appropriate responses to treatment. All three cases subsequently developed isolated elevation of serum methylmalonic acid in the absence of megaloblastic anemia, or alterations in serum vitamin B12 or homocysteine levels. Although none of these patients presented with acute

clinical symptoms of SBBO, each received a seven day course of metronidazole (10 mg/kg/dose twice daily) and exhibited normal MMA concentrations shortly thereafter.

The prevalence of small bowel bacterial overgrowth among patients with SBS is unknown, but may be frequent in those with resected ileocecal valve[13], bacterial dysbiosis, [14] abnormal intestinal motility and intestinal resection[15, 16]. Clinical symptoms may vary in severity making the diagnosis of SBBO challenging in the absence of overt symptoms or small bowel bacterial aspirate[17]. It is hypothesized that propionate, a precursor to MMA, produced by excessive gut bacterial fermentation, is responsible for the elevation in plasma MMA levels[12]. This observation was previously reported in a prospective study documenting increased propionate levels in eleven patients with anatomical lesions such as jejunal diverticulosis, small bowel strictures, and sclerosis of the small bowel predisposing them to malabsorption and loop stagnation. Among this group ten out of eleven patients had a history of bacterial overgrowth, with an observed decline in propionate concentration and clinical symptoms following antibiotic treatment[18].

In our reported case series, there was no small bowel aspirate confirmation of bacterial overgrowth prior to MMA serum level abnormality. However there have been reports of colonic dysbiosis following small bowel resection[19], as well as a predominance of colonic flora in small bowel aspirates in the setting of SBBO[20, 21] suggesting possible retrograde colonic microbial transmission. Given the reported theoretical risk of SBBO in the setting of ileocecal resection, with one study observing a higher predominance of bacterial overgrowth among patients with an absent ileocecal valve[21], our case observations confirm the possible role of altered intestinal microbiota as an etiology of serum MMA elevation.

Another well-documented complication of bacterial overgrowth is competitive bacterial uptake of vitamin B12 that can lead to vitamin B12 malabsorption and deficiency[17, 22]. However, biochemical evidence of vitamin B12 deficiency in the form of low serum vitamin B12 levels was not observed in our cases, likely due to ongoing intramuscular administration of this vitamin, so we are unable to comment on the role of SBBO contributing to B12 malabsorption in these cases.

In summary, serum concentrations of MMA and tHcy have been widely used in the interpretation of vitamin B12 status, along with serum concentrations of vitamin B12 levels. However, our case series suggests that MMA levels should be interpreted with caution in patients with short bowel syndrome who are at-risk for SBBO, and that other potential contributors of elevated MMA levels may need to be considered. Furthermore, our data highlight a potential role for elevated plasma MMA levels as a surrogate marker for SBBO with or without clinical symptoms.

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List of Abbreviations

SBS	Short Bowel Syndrome
MMA	Methylmalonic acid
tHcy	Total homocysteine
SBBO	Small Bowel Bacterial Overgrowth

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Table 1

Laboratory tests before and after 1-week treatment with metronidazole in three children with short bowel syndrome

	Hemoglobin (g/dL)	Mean Cell Volume (fl)	MMA µmol/L	tHcy µmol/L	Vitamin B12 pg/mL
Normal Range	11–14.5	76–90	<0.9	<10	190–778
Case 1					
B12 deficiency diagnosis	12.4	76.7			151
Before Metronidazole	13.6	84.9	1.5	7.7	415
After Metronidazole	13	84.7	0.3	7.4	577
Case 2					
B12 deficiency diagnosis	14.2	81.7	2	11	369
Before Metronidazole	12.7	84.2	6.3	6.7	820
After Metronidazole	13.5	85	<0.1	5.7	811
Case 3					
B12 deficiency diagnosis	14.9	86.3	2.1	11	150
Before Metronidazole	13	83.5	2.5	5.5	336
After Metronidazole	13.6	84.1	0.2	6.5	398