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Juvenile Cobalamin Deficiency in a 17 Year Old Child with Autonomic Dysfunction and Skin Changes

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Abstract

We report a rare case of juvenile cobalamin deficiency who presented at the age of seventeen years. He was underweight and had skin changes, normocytic anemia and autonomic dysfunction which lead to adynamic ileus and acute post-renal failure. The expected macrocytosis was masked by an underlying alpha thalassemia trait. The patient had an excellent response to parenteral cobalamin treatment.

Keywords

Cobalamin; anemia; neuropathy; hypersegmented neutrophils

Introduction

Cobalamin deficiency can develop from acquired causes of intestinal malabsorption or inherited errors of cobalamin absorption or transport[1]. In the Western World the condition is collectively called juvenile cobalamin deficiency (JCD)[2]. This includes the autosomal recessive disorders, Imerslund-Gräsbeck Syndrome (IGS) and intrinsic factor deficiency (IFD)[2]. IGS is caused by mutations in the cubilin (*CUBN*)[3] or the amnionless (*AMN*)[4] gene encoding the proteins that constitute the intrinsic factor-cobalamin receptor “cubam”, found in the mucosa of the terminal ileum[5]. Mutations in the gastric intrinsic factor (*GIF*) gene cause IFD[6]. Patients present with a variety of signs and symptoms including megaloblastic anemia, neurological dysfunction and failure to thrive[7]. In contrast, the cobalamin deficiency is mostly related to poor nutrition or infections in developing countries [8].

We report an unusual case of JCD in an African American adolescent presenting at the age of 17 years with autonomic nervous system dysfunction, skin rash and anemia. His symptoms improved dramatically after starting parenteral cobalamin supplementations.

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Case Report

This 17 year old African American male presented to the emergency room with chief complaints of chronic constipation and worsening abdominal pain for 2 weeks. His last bowel movement was with the help of an enema 3 days ago. He reported having good oral intake and a couple of episodes of emesis associated with his abdominal pain. Past medical history was significant for being born with gastroschisis, status post surgical repair and history of pyeloplasty for bilateral pelviureteric junction obstruction along with left orchiectomy for an undescended testicle at the age of 3 years. He did not have regular medical care, but was up to date with his immunizations. He had a lean build, with both height and weight plotting between 10th and 25th percentiles for age. His scalp hair started turning gray two years ago. Also over the past 2 years he had started noticing dark black hyperpigmented spots on the dorsum and anterior surfaces of his hands and feet (Figure 1). He described his diet to be balanced and denied use of any drugs or medications. His father also had a history of having gray hair at a young age, while a couple of maternal cousins had lupus.

He was afebrile, with no signs of dehydration. The abdomen was flat, with hyperactive bowel sounds and was diffusely tender, without guarding or rebound tenderness. The anterior abdominal wall was loose and had scars from previous surgeries. An abdominal CT scan revealed multiple dilated, fluid filled small bowel loops and abundant stool throughout the colon, suggestive of adynamic ileus. Interestingly, he was also found to have bilateral mild to moderate hydronephrosis and pelvicaliectasis. Laboratory studies revealed blood urea nitrogen of 22mg/dl and serum creatinine of 1.4mg/dl. Electrolytes were within normal limits. Hemoglobin was 7.7g/dl that further dropped down to 6.8g/dl, with normal red blood cell indices and the reticulocyte count was 0.9% (Table I). The rest of the blood counts and the levels of serum bilirubin, lactate dehydrogenase and haptoglobin were within normal limits. His urine analysis showed 3+ proteins but negative for free hemoglobin and bilirubin, on 2 separate occasions, urine pH was between 6.0 and 7.0. It was interesting to note that apparently his baseline hemoglobin had been around 9g/dl but a sudden drop had recently occurred along with the development of renal failure and worsening of the constipation. The serologies for Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus and parvovirus B19, sent as a part of the workup for an aplastic crisis, came back negative.

The peripheral smear showed numerous elliptocytes, no spherocytes but marked anisocytosis. Neutrophils had hypersegmented nuclei and platelets morphology was normal. Upon further investigation, he was found to have extremely low serum cobalamin levels (<150 pg/ml; normal range: 200–835) with normal red blood cell folate levels. Before the cobalamin deficiency was established, he was aggressively hydrated for acute renal failure with no correction of serum creatinine or urine output and had an extensive gastroenterology work-up for constipation. Endoscopy and biopsies from upper and lower gastrointestinal tract showed normal histology. No gastric fluid was saved for IF determination. About 60 hours after admission he was started on 1mg daily cyanocobalamin intramuscular injections. The patient had a dramatic response and within 24 hours his reticulocyte count rose to 9%, his urine output increased, proteinuria resolved, kidney function started to improve and he started having regular bowel movements. After receiving 4 doses the patient was discharged home on biweekly cobalamin injections for a month followed by monthly injections of cobalamin in an out-patient clinic.

He showed significant clinical improvement. His appetite and activity level increased, he gained more than 8 kilograms of body weight over the subsequent 4 months. His hemoglobin corrected to 14g/dL, while mean corpuscular volume (MCV) dropped from 91fL at the time of diagnosis to 75fL (Normal range: 78 – 98). Hemoglobin evaluation

showed low Hemoglobin A2 (1.2%) and alpha-globin gene analysis showed a single gene deletion, which explained why he did not develop macrocytosis in the face of cobalamin deficiency. The ektacytometry showed mildly increased osmotic fragility which could be seen in heterozygous hereditary elliptocytosis. He continues to have occasional hypersegmented neutrophils and rare ovalocytes on peripheral smear. The macular rashes on his hands and feet have also gradually faded away. He continues to have mild residual pelvicaliectasis on imaging studies.

The absence of anti-parietal cell antibodies and a normal stomach biopsy makes pernicious anemia less likely. The DNA samples from the patient, his mother and a half-sibling were studied exon-by exon for mutations in *GIF*, *AMN* and *CUBN* at the Comprehensive Cancer Center, Ohio State University. None of the above mutations were found in any of the family members tested. Thus we also ruled out inherited JCDs. It is therefore still not clear whether cobalamin deficiency is secondary to a genetic or an anatomic abnormality.

Discussion

Cobalamin deficiency is known to cause anemia and neurological abnormalities. Rarely patients may develop autonomic nervous system dysfunction like constipation, orthostatic hypotension, impotence and even urinary stasis[9]. We propose that probably an autonomic dysfunction secondary to cobalamin deficiency lead to this patient's adynamic ileus, and pelvicaliectasis that caused severe constipation and acute non-obstructive post-renal failure. These complaints resolved rapidly once his cobalamin was replaced. Poor weight gain and hyperpigmented macules from cobalamin deficiency have also been reported in the literature, and as expected they started resolving within a few months of treatment[10].

The peripheral smear showed hypersegmented neutrophils which are known to persist for several days during the recovery phase[11]. Apparently our patient had a chronic, compensated anemia with upper normal MCV. Possibly, a viral illness with transient myelosuppression might have exacerbated his condition when he presented to us. As his anemia was corrected in response to treatment with cobalamin, his red blood cells became microcytic, and he was found to have an alpha thalassemia trait. Slightly low MCV is characteristic of single α gene deletion[12]. Thus the normal MCV at the time of diagnosis was actually higher for his baseline. Another common condition in African population, heterozygous hereditary elliptocytosis, would explain the elliptocytes seen on the peripheral smear; this was supported but not confirmed with ektacytometry. If elliptocytosis would be present this could at least contribute to cobalamin deficiency due to a higher turnover and therefor need for nutritional cobalamin substitution.

Skin changes associated with cobalamin deficiency include hyperpigmentation, vitiligo, hair changes and recurrent mouth sores[13]. These changes are usually reversible and can be an important clue towards making an early diagnosis and thus prevent serious complications. The hyperpigmentation is due to increased production of melanin[14] and common sites are dorsum of hands and feet, which was also the case in our patient. These findings are more common in dark skinned patients and cobalamin deficiency should be ruled out.

Another important factor that makes this case unusual is the age of presentation. Patients presenting up to 14 years of age have been reported in the literature[15], but our patient presented rather late for JCD. Apparently his diet was well balanced. His symptoms responded well to parenteral cobalamin supplementation but the cause of malabsorption could not be attributed to either inherited JCD or pernicious anemia. Finally, our patient has a history of surgical repair for gastroschisis performed as an infant. There have been case reports of cobalamin deficiency development secondary to malabsorption after Gastroschisis

repair[16]. Partial ileal resection or non-functioning intestines are possible morbidities of gastroschisis repair[17] and can be contributing to our patient's JCD.

In conclusion, patients with JCD can present, late in adolescence, with a variety of symptoms. Mucocutaneous lesions not responding to conventional therapy could be the earliest sign and the absence of macrocytosis does not always rule out cobalamin deficiency. Although the etiology of JCD is not always identified an excellent response to treatment is anticipated.

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References

1. Whitehead VM. Acquired and inherited disorders of cobalamin and folate in children. *Br J Haematol*. 2006; 134(2):125–136. [PubMed: 16846473]
2. Ament AE, Li Z, Sturm AC, et al. Juvenile cobalamin deficiency in individuals of African ancestry is caused by a founder mutation in the intrinsic factor gene GIF. *Br J Haematol*. 2009; 144(4):622–624. [PubMed: 19036097]
3. Aminoff M, Carter JE, Chadwick RB, et al. Mutations in CUBN, encoding the intrinsic factor-vitamin B12 receptor, cubilin, cause hereditary megaloblastic anaemia 1. *Nat Genet*. 1999; 21(3):309–313. [PubMed: 10080186]
4. Tanner SM, Aminoff M, Wright FA, et al. Amnionless, essential for mouse gastrulation, is mutated in recessive hereditary megaloblastic anemia. *Nat Genet*. 2003; 33(3):426–429. [PubMed: 12590260]
5. Fyfe JC, Madsen M, Hojrup P, et al. The functional cobalamin (vitamin B12)-intrinsic factor receptor is a novel complex of cubilin and amnionless. *Blood*. 2004; 103(5):1573–1579. [PubMed: 14576052]
6. Tanner SM, Li Z, Perko JD, et al. Hereditary juvenile cobalamin deficiency caused by mutations in the intrinsic factor gene. *Proc Natl Acad Sci U S A*. 2005; 102(11):4130–4133. [PubMed: 15738392]
7. AC, A. Hematology Basic principles and practice. 3. Hoffman, RBE.; Shattil, SJ.; Furie, B.; Cohen, HJ., editors. Philadelphia: Churchill Livingstone; 2000. p. 446-485.
8. Iqbal SP, Kakepoto GN. Gastrointestinal abnormalities in vitamin B12 deficient patients with megaloblastic anemia. *J Coll Physicians Surg Pak*. 2009; 19(10):672–673. [PubMed: 19811726]
9. Yagci M, Yamac K, Acar K, et al. Gastric emptying in patients with vitamin B(12) deficiency. *Eur J Nucl Med Mol Imaging*. 2002; 29(9):1125–1127. [PubMed: 12192555]
10. Simsek OP, Gonc N, Gumruk F, et al. A child with vitamin B12 deficiency presenting with pancytopenia and hyperpigmentation. *J Pediatr Hematol Oncol*. 2004; 26(12):834–836. [PubMed: 15591907]
11. Nath BJ, Lindenbaum J. Persistence of neutrophil hypersegmentation during recovery from megaloblastic granulopoiesis. *Ann Intern Med*. 1979; 90(5):757–760. [PubMed: 434675]
12. Stuart, H.; Orkin, DGN., editors. Nathan and Oski's Hematology of Infancy and Childhood. Elsevier; 2009. p. 1047-1048.
13. Kannan R, Ng MJ. Cutaneous lesions and vitamin B12 deficiency: an often-forgotten link. *Can Fam Physician*. 2008; 54(4):529–532. [PubMed: 18413300]
14. Mori K, Ando I, Kukita A. Generalized hyperpigmentation of the skin due to vitamin B12 deficiency. *J Dermatol*. 2001; 28(5):282–285. [PubMed: 11436369]
15. Grasbeck R. Imerslund-Grasbeck syndrome (selective vitamin B12 malabsorption with proteinuria). *Orphanet J Rare Dis*. 2006; 1:17. [PubMed: 16722557]
16. Marsch AF, Shashidhar H, D'Orazio JA. B12 deficient megaloblastic anemia in a toddler with a history of gastroschisis. *J Pediatr*. 158(3):512. [PubMed: 20961567]

17. Schlatter M, Norris K, Uitvlugt N, et al. Improved outcomes in the treatment of gastroschisis using a preformed silo and delayed repair approach. *J Pediatr Surg.* 2003; 38(3):459–464. discussion 459–464. [PubMed: 12632367]

Figure 1.
Hyperpigmented macules seen on the palms at the time of diagnosis (left) and cleared after 2 months of treatment (right)

Table 1

Laboratory Values (MCV: Mean Corpuscular Volume; RBC: Red Blood Cells)

Days From Start of Parenteral Cobalamin	Normal Ranges	Day -5	Day -2	Day -1	Day 0	Day 1	Day 3	Day 9	Day 19	Day 30	Day 51	Day 56	Day 108
Hemoglobin (G/dl)	13 – 16	9.3	7.7	6.8	6.8	7.2	8	10	12.9	13	14.3	13.3	14.5
MCV (fl)	78 – 98	90.6	86.3			90.3	90	90.2	88.8	84.4	80.5	79.4	74.8
Reticulocyte %	0.5 – 1		0.7			9	15.3	7	3.1	1.8		1.2	1
Serum Creatinine (mg/dl)	0.7 – 1.3	0.8	1.4	1.3	1.4	1.1		0.9	0.9	0.8		0.8	0.8
Urine Protein (+)	Negative		3	2									0
Vitamin B12 level (pg/ml)	200 – 835			<150									911
Methylmalonic Acid (microMoles/Lit)	0.08 – 0.56							0.8					
Homocysteine (microMoles/Lit)	2.2 – 13.2												9.1
RBC Folate (ng/ml)	140 – 648			431									351
Iron Profile			Normal		Normal								