

Zinc and biotin deficiencies after pancreaticoduodenectomy

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Abstract

We report zinc and biotin deficiencies after pancreaticoduodenectomy in a 16 year old female presenting clinically with marked alopecia, total body hair loss, dry skin with scales, and maculopathy with significant vision loss. These micronutrient deficiencies likely occurred due to resection of the duodenum and proximal jejunum, sites of primary absorption of several micronutrients and their protein carriers, including zinc and biotin. Early diagnosis is essential to prevent irreversible sequelae. Adequate supplementation of zinc and biotin as well as dietary advice is needed for clinical improvement. (*Acta gastroenterol. belg.*, 2010, 73, 283-286).

Key words: pancreaticoduodenectomy, Zinc & Biotin deficiency, maculopathy.

Introduction

Whipple operation or pancreaticoduodenectomy (PD) is a major surgery performed to treat tumors of the exocrine pancreas. It involves removal of the head of pancreas and sometimes the body as well, along with the duodenum. Micronutrient deficiency has been reported in a few studies after Whipple procedure (1,2). This occurs due to the removal of the duodenum and proximal jejunum, sites of primary absorption of several micronutrients, particularly zinc (3).

Biotin deficiency is a rare nutritional disorder of multiple etiologies characterized clinically by physical manifestations affecting the skin, hair, central and peripheral nervous system and intestinal tract (4).

We report here the case of a 16 year old female, followed at the American University of Beirut Medical Center, who presented 3 years after her Whipple procedure, with biotin and zinc deficiency. It was manifested clinically by marked alopecia, total body hair loss, dry skin with scales, and maculopathy with significant vision loss.

Of note, zinc deficiency after PD has been reported presenting with acrodermatitis enteropathica (5,6). However, to our knowledge, no previous reports have described combined biotin and zinc deficiency after PD. Recognition of the risk for multiple micronutrient deficiencies in such patients is essential for proper treatment.

Case report

The patient is a 16 year old post pubertal female who was formerly diagnosed to have a papillary tumor of

head of the pancreas consistent with a solid tumor of low malignant potential. The patient underwent Whipple surgery three years prior to presentation after which no radiation or chemotherapy was required. On follow-up, a series of computed tomography (CT) scans of the abdomen and pelvis were done regularly to assess disease status. As part of post-pancreatectomy follow-up, lab tests were done every three months. Those included the pancreatic enzymes amylase and lipase, as well as fat-soluble vitamin serum levels, and fecal fat testing. The patient was also followed regularly by a dietitian and had been gaining weight adequately.

Four months prior to her current presentation, the patient started complaining of intermittent episodes of vomiting undigested food, averaging three per week. She also developed marked progressive alopecia and total body hair loss along with generalized dry scaling skin, and a maculopapular rash with skin peeling. On presentation, she also reported secondary amenorrhea of four months duration, with a 4 kg weight loss (BMI dropped from the 50th percentile before surgery to below the 5th percentile at presentation), fatigue and decreased exercise tolerance. She had been maintained on 5000 IU/day of vitamin A, 400 IU/day of vitamin E and 800 IU/day of vitamin D supplementation after documentation of low serum levels. A CT scan of the abdomen done one month prior to presentation showed no abnormality except for low hepatic signal intensity compatible with fatty liver.

On physical examination, she appeared tired and emaciated. Her height, weight and body mass index were 156 cm (at the 10th percentile), 39 kg (below the 5th percentile) and 16 kg/m² (below the 5th percentile), respectively. Her abdomen was soft with no hepatosplenomegaly. The most striking findings were severely dry skin with scaly papules over the trunk and extremities that had evolved focally into vesicubullous erosive lesions, mainly on the distal extremities. This later progressed to peeling of the skin over the palms and soles. She also had diffuse hair loss and a raw red tongue (Fig. 1, panels a-d).

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Fig. 1. — a. Vesiculobullous erosive lesions around the mouth ; b. Alopecia ; c. Dry skin with scaly papules ; d. Peeling of the skin over the soles ; e-g : Improvement after treatment.

Laboratory evaluation was significant for the following : hemoglobin 10.3 g/dL ; hematocrit 30%, MCV 87 fl, total protein of 67 g/L, Alb/Glob of 25/42 ; fasting morning zinc 42 µg/dL (NI 70-150) ; biotin 86 pg/mL (NI > 200) and 25-hydroxyl-Vitamin D3 of 12.5 ng/mL (NI 20-60). Vitamin A 322 ng/mL (NI 200-1200), Vitamin E 6.3 µg/mL (NI 5-18), Vitamin B2 298 µg/L (NI 180-295), Vitamin B6 17.4 ng/mL (NI 3.6-18), Vitamin B12 1121 pg/m (NI 223-1132), folate 18.8 ng/mL (NI 4.2-19.9) and selenium 73 µg/L (NI 55-103), amylase 34 IU/L (NI 10-120), lipase 17 U/L (NI 13-60), liver enzymes including SGPT 51 IU/L (NI 0-50), SGOT 53 IU/L (NI 0-50), Alkaline Phosphatase (ALP) 150 IU/L (NI 26-235), γ-GT 50 IU/L (10-50), Bilirubin T/D 0.6/0.3 (NI 0.0-1.2/0.0-0.3), TSH 3.130 µU/mL (NI 0.3-5) and INR 1.2 (NI 0.85-1.2), were all normal. In addition a fecal fat stain was done and was positive. CT of the abdomen, and an upper GI series with small bowel follow-through were normal, ruling out any tumor recurrence. An ophthalmologic evaluation revealed 20/200 vision in both eyes, and an atrophic macula.

Based on the clinical findings and laboratory data, the diagnosis of a combined biotin and zinc deficiency with acrodermatitis enteropathica was made. The patient was

hospitalized and treated with intravenous biotin and zinc. She also received enteral nutritional support, and pancreatic enzyme supplements with meals. Her vomiting improved progressively as well as her appetite and she was able to tolerate full meals. In addition, aggressive wound care and application of topical emollients were used for the areas of peeling skin. After one week of hospitalization, the patient was discharged home on oral zinc and biotin supplementation (biotin 10 mg/day and zinc sulfate 50 mg/day), and continued on pancreatic enzyme supplementation with meals. Over the following three months, a striking improvement was seen with 100% re-epithelialization of the skin lesions, resolution of the glossitis and alopecia and marked improvement in vision (Fig. 1, panels e-g). Currently she is maintained on pancreatic enzymes and multivitamin preparation.

Discussion

Quality of life and postoperative outcome after PD have been well described (7). However few reports discuss the deficiency of specific micronutrients such as Zinc after such a procedure (5,6). To our knowledge, no reports describe biotin deficiency along with zinc deficiency after PD, with severe clinical manifestations such as vision loss. Our report highlights the importance of evaluating both vitamin and mineral deficiencies in such patients, especially since the serious sequelae such as vision loss may be irreversible.

Prasad *et al.* (8) was the first to report zinc deficiency in humans. Prasad (8) defined severe or clinical zinc deficiency as a condition characterized by short stature, hypogonadism, impaired immune function, skin disorders, cognitive dysfunction and anorexia. Other clinical manifestations of zinc deficiency include dermatitis with dry scaly erythematous lesions, cheilitis, angular stomatitis, and nail dystrophy. Although diarrhea can occur, it may be intermittent or totally absent (9). Hereditary zinc deficiency is thought to result from an abnormality in the zinc transporter (9). Acquired zinc deficiency is usually due either to inadequate zinc intake, malabsorption, or low zinc storage. Some causes of acquired zinc deficiency are short bowel syndrome, Crohn's disease, cystic fibrosis (10,11), infections, food allergy, eating disorders and a rare inborn error of metabolism (non-ketotic hyperglycemia) (5).

Zinc deficiency has been reported after PD, presenting with an acrodermatitis enteropathica-like eruption in 2 patients. Both patients had alopecia, glossitis and nail dystrophy (6). Similarly, Suchithra *et al.* (5) reported acrodermatitis enteropathica-like skin eruption due to zinc deficiency in a patient with short bowel syndrome after jejuno-transverse colon anastomosis. Armstrong *et al.* (2) reported combined zinc and iron deficiency in five out of ten patients who had undergone PD for malignant disease, despite adequate intake. However, none of the described patients presented with biotin deficiency, or decreased vision and maculopathy.

Multiple reasons may account for zinc deficiency after PD. One is a disturbance in the absorption of zinc in the jejunum, which is commonly resected during the Whipple procedure. Another is poor protein absorption after PD. This is because zinc is transported in serum via carrier proteins, namely albumin (57% of serum zinc), alpha-2-macroglobin (40%) and amino acids such as histidine and cysteine (<3%) (6). As a consequence poor protein absorption may cause low zinc availability. In addition fractional absorption of zinc is impaired by pancreatic insufficiency and is improved by exocrine pancreatic replacement (12). Moreover, deficiencies in branched chain amino acids and essential fatty acids may contribute to the formation of skin lesion similar to that of acrodermatitis enteropathica seen in patients with zinc deficiency (13,14).

Biotin is an essential cofactor for multiple metabolic pathways such as gluconeogenesis, amino acid catabolism and fatty acid synthesis. Regardless of the etiology of biotin deficiency, the clinical manifestations affect the skin, central and peripheral nervous systems and intestinal tract. Dry skin, seborrheic dermatitis, as well as alopecia have been reported (15). In addition, myalgias, hyperesthesias and paresthesias are commonly reported in biotin deficient patients, also sensorineural hearing loss can develop after biotinidase deficiency (16).

Causes of biotin deficiency are varied. It has been reported in patients maintained on anticonvulsant therapy, who present with biotin – responsive basal ganglia disease. Biotin deficiency can occur in association with inborn errors of metabolism. It may develop after prolonged oral antibiotic therapy, or in patients maintained on total parenteral nutrition without biotin supplementation (4). Also, a novel E64K mutation has been reported in a patient with partial biotinidase deficiency. The mutation may have been the cause behind the deficiency and the clinical symptoms (developmental delay, hypotonia, seizures and infantile spasms without alopecia or dermatitis) observed in the patient (17).

Two case reports have described acquired biotin deficiency in children. Fujimoto *et al.* (18), described a 5 month old infant with periorificial erythematous, scaly eruption involving the diaper area and scalp, along with alopecia. The infant had “dyspepsia” and had been fed an amino acid formula since 4 weeks of age. Kimura *et al.* (19) reported a 5 year old boy requiring tube feeding since birth due to congenital central nervous system abnormalities. The child presented with alopecia and an eczematous eruption. The cutaneous findings responded to Biotin supplementation. To our knowledge, only one report described a combined zinc and biotin deficiency, in a premature hypotrophic infant after 4 months of parenteral nutrition. The clinical manifestations were similar for these deficiencies and included dermatitis, alopecia and susceptibility to infection (20). Unlike our patient, the deficiencies in this infant occurred due to prolonged parenteral nutrition, and no ophthalmic manifestations were reported.

Biotin is absorbed in the intestine through a sodium dependent carrier mediated system called the sodium dependent multivitamin transporter (SMVT). Biotin absorption in the intestine is regulated by intracellular factors such as protein kinase C and calcium/calmodulin-mediated pathways (21,22), and extra cellular factors such as extra cellular biotin levels and transcriptional regulatory mechanisms (23). Any disruption of these processes can lead to biotin deficiency. Alternatively, abnormalities in biotinidase, an enzyme required for the conversion of biocytin to biotin, can also lead to biotin deficiency. For instance, decreased biotinidase in pancreatic secretions can lead to inadequate secretions of protein-bound biotin, affecting the gastrointestinal absorption of biotin. Secondly, biotin salvage may be impaired during normal protein turnover to which biotin is covalently linked (24). Thirdly, abnormal increase in renal loss of biotin and biocytin can lead to deficiency in biotin (24).

One or a combination of these mechanisms may have lead to biotin deficiency after PD in our patient. Most likely, the reduction of the absorptive area due to the resection of a portion of the jejunum during the PD resulted in a decrease of both zinc and biotin absorption leading to both zinc and biotin deficiency as well as other vitamin deficiencies.

Maculopathy and decreased vision were observed in our patient. Notably, there have been no reports of electroretinographic abnormalities secondary to biotin deficiency in the literature, whereas optical atrophy has been described in biotinidase-deficient patients (25). Zinc deficiency can cause corneal oedema that may progress to corneal opacity (24). It can also lead to dry conjunctivitis that could develop into xerosis and keratomalacia. Scotopic ERG abnormalities and night blindness have also been associated with low zinc levels (26), and zinc deficiency can contribute to age-related macular degeneration (ARMD). The mechanism is still uncertain ; however, zinc depletion has been reported to induce-macromolecule synthesis and caspase dependent apoptosis of cultured retinal cells (27). In addition, zinc status influences several aspects of vitamin A metabolism, including its absorption, transport and utilization. Zinc is a component of retinol-binding protein, a protein necessary for transporting vitamin A in the blood. Even with normal vitamin A levels zinc deficiency can reduce the activity of alcohol dehydrogenase, the enzyme that converts retinol to retinal, this latter form of vitamin A is necessary for the synthesis of rhodopsin, a protein in the eye that absorbs light and that is involved in dark adaptation (28,29).

Our patient also had fatty liver noted on CT of abdomen. Although workup did not reveal a specific etiology, a recent report showed a 37% incidence of fatty liver post-PD. The authors hypothesized that fatty liver in these cases may indirectly be related to zinc deficiency. In their opinion, major pancreatectomy may cause marginal zinc deficiency, leading to persistent postoperative

diarrhea. This then induces impairment of the gut barrier by damaging the tight junctions and the epithelium of the enteric villi, resulting in bacterial and endotoxin translocation. Kupffer cells in the liver are subsequently activated by endotoxin from portal vein blood, phagocytize fat droplets, leading to fatty liver (30).

In conclusion, the presented case shows that zinc deficiency along with biotin deficiency may develop after PD, likely due to malabsorption as well as deficiency in protein carriers of both zinc and biotin. This may result in both life- and vision- threatening complications. Early diagnosis is essential to prevent irreversible sequelae. In addition to monitoring of serum levels of fat-soluble vitamins (A, D, E) and K (INR) in these patients, it may be prudent to monitor micronutrient levels, specifically biotin, zinc, and selenium, at frequent intervals. Importantly, a detailed nutritional history and physical exam should be performed at each follow-up, including an ophthalmologic examination for early detection of visual changes related to nutritional deficiencies. This is particularly important to allow early intervention before vision loss is irreversible. In patients with proven deficiencies, adequate supplementation of micronutrients and vitamins as well as dietary advice is needed for clinical improvement. Advice on compliance, especially in teenage patients, is critical for prevention of relapse.

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