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Malabsorption in Marfan (Ehlers-Danlos) Syndrome

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ABSTRACT

A patient with somatic features of both Marfan and Ehlers-Danlos syndromes presented with severe intestinal malabsorption. Functional intestinal abnormalities were thought to be due to bacterial overgrowth associated with small intestinal hypomotility and giant jejunal diverticula. The structural intestinal defects are presumed to be the result of defective collagen synthesis in these hereditary connective tissue disorders.

Introduction

The classic manifestations of Marfan syndrome include arachnodactyly, dolichostenomelia (limbs inappropriately long as compared with the trunk), mild joint laxity, aneurysm of the ascending aorta, aortic regurgitation, ectopia lentis, and recurrent femoral, inguinal, and diaphragmatic hernias.[1] Gastrointestinal complications have been reported rarely, notably intestinal diverticula and spontaneous pneumoperitoneum.[2-5]

We describe a patient with the somatic manifestations of Marfan syndrome who, in addition, had clinical features suggesting Ehlers-Danlos syndrome. He presented with clinical and biochemical evidence of intestinal malabsorption, and radiologic examination demonstrated multiple giant jejunal diverticula, with generalized atony of the gastrointestinal tract. We believe this is the first report of malabsorption resulting from intestinal abnormalities associated with either of these heredity connective tissue disorders.

History

A 41-year-old white man was investigated for a 20-lb. weight loss and abdominal discomfort. Recurrent attacks of abdominal pain had occurred with increasing frequency over the previous 15 years with two or three loose bowel actions per day. The patient was tall (6'3"), and thin (145 lbs.), with dolichostenomelia and arachnodactyly (crown-pubis/pubis-heel ratio = 0.82 $N > 0.92$), together with a high-arched palate, blue sclerae, and severe myopia. In addition, he demonstrated clinical features suggesting the Ehlers-Danlos syndrome including markedly hypermobile joints, cigarette paper scars, soft fleshy skin tags, and skin hyperelasticity. Systemic examination was unremarkable apart from a soft aortic systolic murmur. He had undergone previous bilateral inguinal and femoral hernia repairs. Although Marfan syndrome had not been clearly documented in the patient's parents or siblings, both his father and his sister had died at relatively young ages from

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strangulated hernia. Two of the patient's own sons and two nephews were of Marfanoid appearance with arachnodactyly.

An exploratory laparotomy had been performed elsewhere 3 months before, and multiple large wide-mouthed diverticula of the jejunum had been observed, measuring up to 8 cm in diameter. The entire small and large bowel was dilated and flaccid, and the mesenteries of both the sigmoid and cecum were long and mobile. A cecopexy and sigmoidopexy were performed. Several "grape-like" cystic structures removed from the region of the gastrosplenic ligament showed the pathological appearance of pneumatosis cystoides intestinalis.

Laboratory results included the following: hemoglobin, red cell indices, white cell count, and differential were normal; serum albumin 3.1 g%, globulin 2.5 g%, serum iron 50 mg% (normal rangae (NR), 75–150), total iron binding capacity 270 mg% (NR, 275–375); serum carotene 13 mg% (NR, 50–200); urinary xylose excretion 2.7 g in 5 hours (NR, 5.3–7.7); fecal fat 34 g in 24 hours (NR <6); serum B_{12} <20 pg/ml (NR, 150–900); and serum folate >30 ng/ml (NR, 5–24). A Schilling test demonstrated excretion of 1.7% of injected B_{12} (NR, 7.5%), which rose to 6.9% with intrinsic factor. Serum amylase was normal. A small bowel biopsy was mildly abnormal showing slight blunting of the villous architecture with a loose edematous texture of the lamina propria.

Radiologic examination of the upper gastrointestinal tract showed a large paraesophageal hiatal hernia with redundancy and dilatation of the esophagus, and a high transverse stomach. The entire small bowel was markedly dilated and atonic and multiple wide-mouthed giant diverticula were seen in the jejunum (Figs. 1 and 2). A barium enema showed generalized loss of haustration throughout a large, dilated, redundant colon with a high mobile cecum (Fig. 3). Radiologic examination of the hands demonstrated a metacarpal index of 9.2 (NR, 5.9–8.4), indicating arachnodactyly of a degree diagnostic of Marfan syndrome (Fig. 4). During the course of his hospital admission, the patient suffered one of his characteristic attacks of pain which proved to be associated with pneumoperitoneum (Fig. 5). Symptoms spontaneously abated and there was no surgical intervention. The discharge diagnosis was of Marfan syndrome complicated by malabsorption. This was considered to be the result of bacterial overgrowth in large jejunal diverticula and hypotonic bowel.

The following year, the patient was readmitted with a further attack of severe abdominal pain. On admission he was found to be in hypotensive shock and died shortly after. Autopsy revealed infarction of almost the entire ileum with a long and edematous mesentery which had undergone torsion. The multiple large jejunal diverticula and generalized dilatation of the bowel were confirmed. No aortic aneurysm was observed.

All of the patient's five children are under the age of 25 years and have been examined radiologically, including barium studies of the entire gastrointestinal tract, and followed over a 10-year period. Although two sons have the skeletal manifestations of Marfan syndrome and one has had inguinal herniorrhaphies, none have any symptoms of malabsorption or radiologic abnormalities of the gastrointestinal tract at this time.

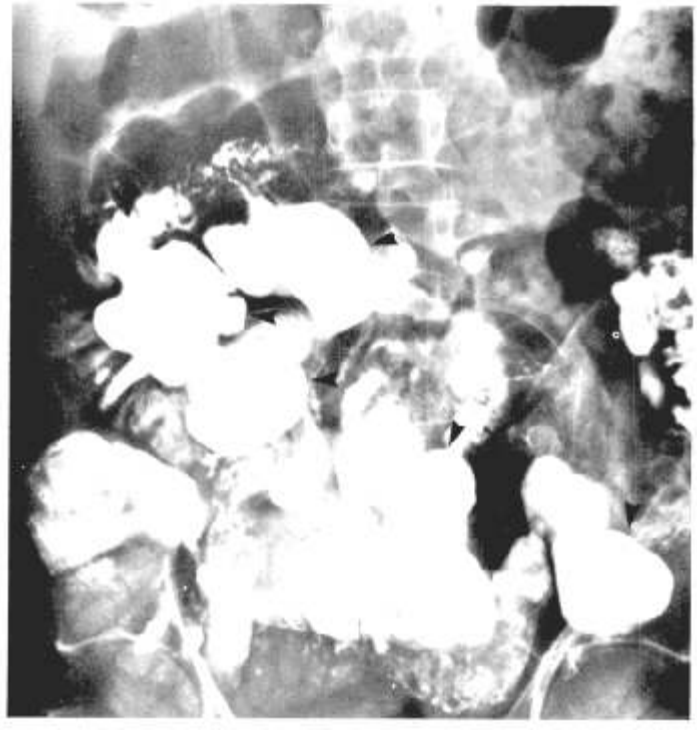

Figure 1. Barium follow-through examination showing greatly dilated small intestine and multiple barium-filled diverticula (arrowheads).

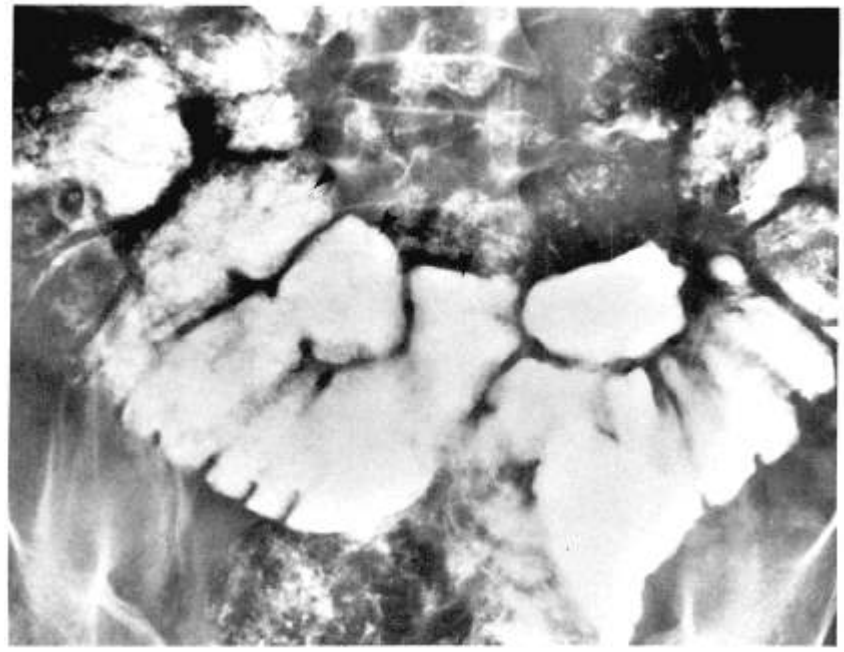

Figure 2. Dilated loop of jejunum showing multiple wide-mouthed jejunal diverticula (arrowheads).

Discussion

We have described a patient with somatic features of both Marfan and Ehlers–Danlos syndrome with clinical and biochemical evidence of malabsorption. The presence of multiple giant jejunal diverticula and generalized bowel atony indirectly suggest bacterial overgrowth as the most likely cause for malabsorption. This is supported by the low serum B_{12} concentration, impaired intestinal B_{12} absorption, and elevated serum folate.[6,7] The increase in vitamin B_{12} absorption after administration with intrinsic factor

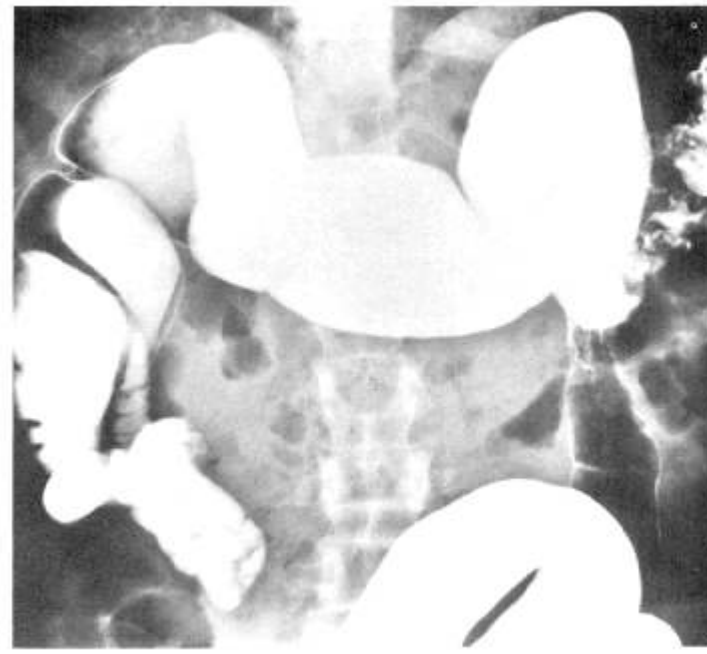

Figure 3. Barium enema showing dilated, ahaustral, and redundant colon.

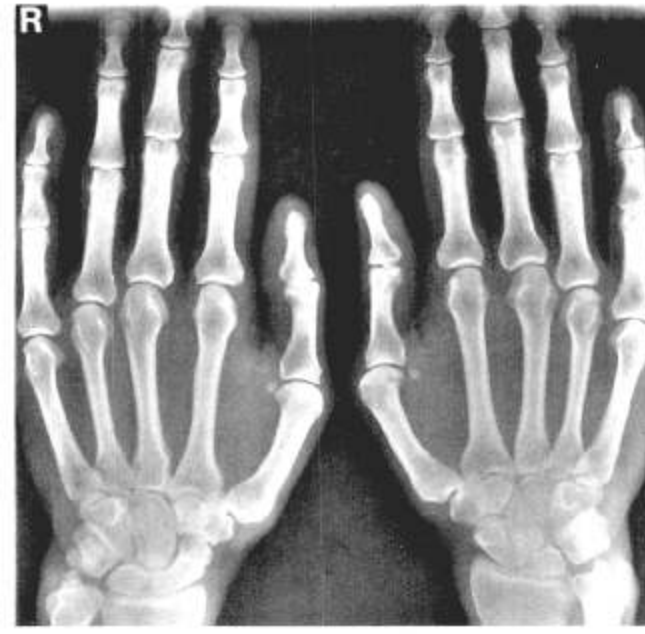

Figure 4. Hands demonstrating arachnodactyly. Metacarpal index = 9.2 (NR, 5.9–8.4).

may indicate early pernicious anaemia, although the rise remains suboptimal and probably reflects diminished susceptibility of the intrinsic factor—vitamin B_{12} complex to uptake by intestinal bacterial.[8]

Although gastrointestinal abnormalities are rare in Marfan syndrome, an association with visceral diverticula was first suggested by Clunie and Mason.[2] They described a family of four with small and large bowel diverticula, two of whom had skeletal and ocular manifestations of Marfan syndrome. In three patients, spontaneous perforation of a diverticulum occurred and one also had vesical diverticula. The association of spontaneous pneumoperitoneum with jejunal diverticulosis is often related to the presence of cystic pneumatosis as occurred in our patient.[9] Intestinal diverticula and spontaneous perforation are also features of Ehlers–Danlos syndrome, in which gastrointestinal complications are more common.[10] Our patient demonstrated generalized intestinal atony with megaesophagus and megacolon, both of which are features of this disorder. Massive gastrointestinal hemorrhage and small bowel volvulus are also described.

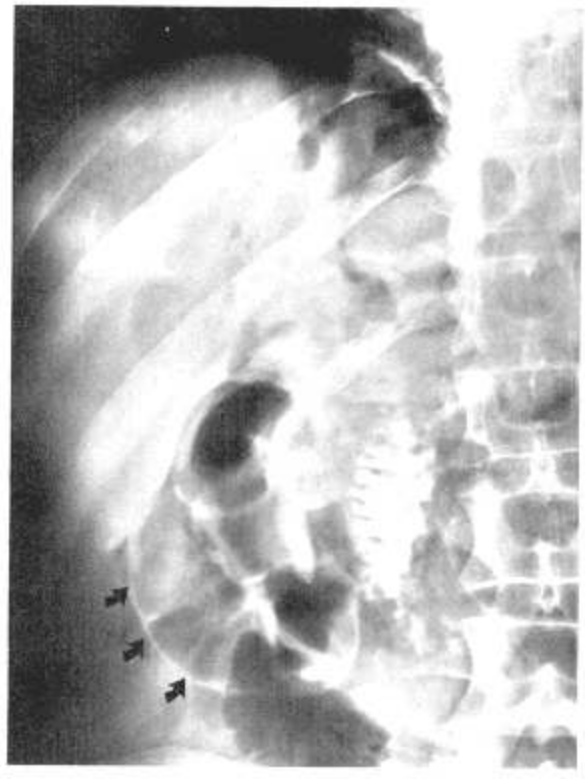

Figure 5. Pneumoperitoneum as shown by subdiaphragmatic gas and the outlining of bowel loops (arrows).

The basic defect underlying Marfan syndrome is unknown, but it seems likely that several different genetic mutations may result in the Marfan phenotype.[11] Abnormalities have been found in the hydroxylysyl intermolecular cross-links in collagen, leading to defective maturation and fiber instability.[12] The ratio of Type I and Type II collagen may also be important, such that a lack of Type I collagen in the aorta is the probable cause of weakness in the vessel wall.[13] Specific abnormalities of the $\alpha 2$(I) chain have been found in both Marfan and a form of Ehlers–Danlos syndrome.[11] The latter is now recognized as a heterogenous disorder, and specific deficiencies of cross-linking and peptide cleavage enzymes have been

recognized in four of the eight disease subgroups.[14] Those groups where enzymatic defects have been identified tend to be inherited as autosomal recessive, whereas the structural defect in the autosomal dominant groups has not been elucidated.

The coexistence of Marfan and Ehlers-Danlos syndromes has been described occasionally.[15-17] These syndromes have several common features including hyperextensibility of joints, high arched palate, blue sclerae, and recurrent internal and external hernias.[1] Intestinal diverticula may be included amongst these shared features. The failure of transmission of features of the Ehlers-Danlos syndrome or any demonstrable gastrointestinal abnormality to our patient's children suggests a recessive form of Ehlers-Danlos, while the phenotype of Marfan syndrome have appeared in the next generation.

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