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Gastrointestinal complications of the Ehlers-Danlos syndrome

PETER H. BEIGHTON[1], J. LAMONT MURDOCH[2], AND THEODORE VOTTELER[3]

From Johns Hopkins Hospital, Baltimore, USA

SUMMARY The gastrointestinal abnormalities encountered in 125 patients with the Ehlers-Danlos syndrome have been described. Spontaneous perforation of the intestine and massive gastrointestinal haemorrhage are uncommon but potentially lethal complications of the Ehlers-Danlos syndrome. Less dangerous abnormalities, such as external hernia, hiatus hernia, eventration of the diaphragm, intestinal diverticula, and rectal prolapse were all encountered in patients in the series. Abdominal surgery in affected patients may be made difficult by fragility of tissues and a bleeding tendency. In the postoperative period, tearing out of sutures and wound dehiscence may occur.

Although the Ehlers-Danlos syndrome is uncommon, affected individuals may be readily recognized by the hypermobility of the joints, the hyperextensibility of the skin, and the wide, thin scars that frequently overlie the bony prominences.

The fragility and laxity of tissue are not confined to the dermis, and the gastrointestinal tract may also be involved. These features, together with a bleeding tendency of variable severity, place patients at risk from a variety of gastrointestinal complications.

In a survey in England, the USA, and Canada, 125 patients with the Ehlers-Danlos syndrome were examined (Beighton, 1970). The purpose of this paper is to discuss the gastrointestinal complications that occurred in these individuals. Spontaneous intestinal perforation is a rare but dangerous complication of the syndrome, and two patients in whom abdominal emergencies took place are described in detail to illustrate a possible mechanism for this hazard.

PRESENT INVESTIGATION

The most important gastrointestinal complications which occurred in the patients in the series were intestinal perforation and haemorrhage. However, these complications were infrequent. Structural abnormalities were much more common but considerably less dangerous (Tables I and II).

TABLE I

GASTROINTESTINAL COMPLICATIONS IN 125 PATIENTS WITH THE EHLERS-DANLOS SYNDROME

Complication		*Number of Patients*
Bleeding		
Severe haematemesis and melaena		6
Peptic ulceration	3	
Hiatus hernia	1	
No demonstrable lesion	2	
Melaena from colonic diverticula		2
External haemorrhoids		8
Skin splitting at the anal margin		5
Jejunal intramural haemorrhage		1
Perforation of the colon (spontaneous)		1
Intestinal obstruction (strangulated femoral hernia)		1
Prolapse of the rectum during infancy		4
Stuctural abnormalities before operative repair		
Bilateral inguinal hernia		3
Unilateral inguinal hernia		9
Unilateral femoral hernia		2
Umbilical hernia		10
Incisional hernia in old abdominal operation scar		2

Gastrointestinal bleeding occurred in eight patients. Of these, six had severe haematemesis and melaena. In one of them this was associated with a hiatus hernia, while peptic ulceration, which was probably unrelated to the Ehlers-Danlos syndrome, was incriminated in three others. In the remaining two, bleeding of moderate severity occurred in the absence of any demonstrable lesion.

Two other patients had milder episodes of melaena which were attributed to colonic diverticula.

Present addresses:
[1]St Thomas' Hospital, London, SE1
[2]Loma Linda Hospital, California, USA
[3]Dallas, Texas

TABLE II

GASTROINTESTINAL ABNORMALITIES REVEALED BY RADIOLOGICAL INVESTIGATION

Radiological Abnormality	*Number of Patients*
Routine chest radiograph (40 patients)	
Eventration of the diaphragm	1
Barium meal for epigastric discomfort (11 patients)	
Hiatus hernia	3
Gastric diverticula	1
Duodenal and jejunal diverticula	1
Barium enema (3 patients)	
Multiple colonic diverticula	

Minor haemorrhage from external haemorrhoids occurred in eight individuals, while a further five noticed bleeding when the skin of the anal margin split during the passage of a hard stool.

Two episodes of spontaneous colonic perforation occurred in a young woman. This patient, and another girl who underwent laparotomy which revealed severe bleeding into the wall of the jejunum, are described in detail in the case reports.

One patient experienced intestinal obstruction, due to strangulation of a femoral hernia. Several other patients reported recurrent, vague, ill-defined abdominal pains. These had been thought to represent episodes of partial obstruction due to intussusception or volvulus but there was no definite evidence to support this viewpoint.

Forty of the patients had a routine chest radiograph, and in these individuals eventration of the diaphragm was demonstrated in one, a middle-aged woman. This abnormality produced no symptoms.

Routine barium studies were not carried out on the patients in the series, but 11 of them previously had had barium meals for epigastric discomfort. Of these, three middle-aged women had been shown to have a hiatus hernia. Their symptoms were mild and responded to conservative treatment. Gastric diverticula had been demonstrated in one patient while duodenal and jejunal diverticula were present in a second patient. Of the three patients who had barium enemata, two were shown to have multiple colonic diverticula.

Repeated prolapse of the rectum had occurred during infancy in four of the patients, but they were all free from this complication by the age of 4 or 5 years.

External herniae were frequently encountered, and, before operative repair, three patients had bilateral inguinal herniae while nine had unilateral inguinal herniae. Similarly two patients had femoral herniae, 10 had umbilical herniae, and two had incisional herniae in the scars of previous abdominal operations.

Two patients had operations for peptic ulcers. These operations were difficult because of the fragility of the tissue but the final results were satisfactory.

In addition to the individuals in the series, the affected father of one patient perished from massive gastrointestinal bleeding, while her brother died, at the age of 32, from a perforation of the bowel. This happened when he jumped off a chair and landed heavily on his heels. Perforation had also taken place in two other individuals who had died before the investigation began, and were not related to the patients seen during the survey.

CASE REPORTS

CASE 1 L.P. (JHH 1121524), an unmarried white school teacher, was born prematurely in 1935. Her precise birthweight was unknown, but she had been a small baby. Bilateral talipes equino-varus deformities of the feet were noted at the time of her birth, and these were subsequently corrected at operation.

As her childhood progressed, dermal fragility contributed to the formation of papyraceous scars. However, this facet of her condition was overshadowed by a severe bruising diathesis. The slightest trauma caused large cutaneous ecchymoses, and haematomata frequently developed. On one occasion, she was confined to bed with a large haematoma in the left calf muscle, after she had marched in a parade. In spite of this bleeding tendency, extraction of teeth had been uneventful, and her menses were normal in quantity and duration.

Although the joints were only moderately hyperextensible, she had experienced recurrent dislocations of the right shoulder, while the left knee joint frequently 'locked', possibly due to displacement of the lateral cartilage.

In 1959 she passed a quantity of bright red blood per rectum, and a few hours later experienced severe abdominal pain. At laparotomy, a rent in the sigmoid was observed. This lesion was 3 in. in length, and involved all layers of the intestinal wall. The surgeon commented upon the remarkable fragility of all the tissues, which cut without any apparent resistance, and recorded that a considerable amount of bleeding took place from all layers of the abdominal wall. A colostomy was fashioned with some difficulty, as the sutures tore out of the bowel wall 'as easily as if it had been fatty tissue'. Subsequent progress was uneventful, and the colostomy was closed nine months later.

In 1961 a further episode of rectal bleeding preceded a second colonic perforation. On this occasion, a round hole, a quarter of an inch in diameter, was located in the sigmoid colon, proximal to the previous lesion. The operation was complicated by bleeding and tissue friability, and on the eighth postoperative day, a quantity of pus was evacuated transvaginally from the pouch of Douglas. She eventually recovered completely, but the abdominal operation scars became distracted.

In 1965 severe headache led to the diagnosis of a subarachnoid haemorrhage. Angiographic investigations were not carried out, because of the dangers of vascular fragility. Once again, recovery was complete.

Her parents and two elder sisters were normal, and none of the other members of the kindred had any stigmata of the Ehlers-Danlos syndrome. There was no known consanguinity in the family.

Examination revealed a pleasant young woman, of normal physique. Her height was 5 ft 5 in., and her weight 130 lb. Her skin was extremely thin, and the subcutaneous venous plexus was very prominent. She had no dermal hyperextensibility, but the forehead and knees bore a few papyraceous scars. The operation scars on the abdomen were wide, and keloid had formed at this site. A number of the cicatrices were darkly pigmented and her limbs bore many bruises.

The finger joints were moderately hyperextensible, and the knees and elbow joints could be extended to 190 degrees. The range of movements of other joints was normal, and articular laxity was not a prominent feature. Varicose veins were present in the legs, but apart from her deformed feet, the rest of the physical examination was unremarkable.

CASE 2 E.A. (JHH 1287186), a white girl born in June 1949, was the product of a full-term pregnancy. Her birthweight was only 5 lb, and, although the membranes had ruptured prematurely, delivery was uncomplicated.

At 7 weeks of age pyloric stenosis was corrected surgically. Recovery was uncomplicated. She was evaluated for easy bruising when she was 10 months old but no diagnosis was made at that time. During childhood she required many sutures for multiple lacerations which resulted from minor trauma. At 11 years of age she ruptured her spleen in a fall from her bicycle and splenectomy was performed.

At the age of 17 a mild gastroenteritis was followed after an interval of three weeks by severe abdominal pain. Surgery was not undertaken but a barium enema subsequently revealed narrowing of the distal colon.

At 19 years of age a second attack of excruciating abdominal pain developed while the patient was sitting quietly at home. She was admitted to hospital immediately and laparotomy was performed. A massive intramural haematoma was present in the jejunum and bleeding into the peritoneal cavity had occurred from this site. A segment of jejunum, 18 in. long, was resected and during this operation the narrowed area in the colon which had been demonstrated radiologically two years previously was examined. Mural fibrosis was observed in this region and it was concluded that the previous episode had also been an intramural haematoma which had not ruptured into either the lumen of the gut or the peritoneal cavity.

Her father was 29 and her mother 33 years of age at the time of her birth. She had four normal brothers, and there was neither parental consanguinity nor any family history of the Ehlers-Danlos syndrome.

Physical examination in 1968, when she was 19 years old, showed a thin, pleasant white girl with a fading subconjunctival haemorrhage in the left eye. The venous plexus was very prominent in the sparse subcutaneous tissue and her thin, translucent skin had the texture of wet leather. She had multiple scars over the knees and shins and acrocyanosis was present. The skin of the palms was finely wrinkled but she had only a moderate degree of dermal hyperextensibility.

The joints were not hyperextensible, except for the elbows, which could be extended to 190°.

A systolic ejection murmur was heard in the pulmonic area. The second sound was normally split.

With the exception of the scarred abdomen, the rest of the physical examination was normal.

DISCUSSION

Spontaneous intestinal perforation is a rare but dangerous hazard in the Ehlers-Danlos syndrome, and there have been several other descriptions of similar catastrophes. A young Frenchwoman, reported by André, Duhamel, Vergos, and Lavallee (1965) had a spontaneous intestinal perforation during childhood, followed by many haemorrhagic episodes, including persistent severe rectal bleeding, a haemoperitoneum from a ruptured ovarian cyst, and a haemothorax. McKusick (1966) mentioned a boy who survived a number of episodes of spontaneous perforation of the colon, only to die at the age of 14 from a dissection of the aorta. Spontaneous perforation of the sigmoid colon occurred in a young woman who was described by Aldridge (1967). She was operated on successfully, but she died from a second perforation three years later. In all these patients, great difficulties were encountered at operation, due to bleeding and friability of the tissues.

The cause of these perforations was unknown, but Aldridge (1967), reporting a further patient with a perforation of the jejunum, made the interesting observation that the lesion occurred both in the apparently normal bowel and at the site of diverticula.

Alimentary bleeding preceded the perforation in several of these individuals, and in view of the changes which were disclosed at operation in case 2, it seems possible that bleeding into the wall of the gut might precede local necrosis and subsequent perforation. This hypothesis is supported by the findings of Epstein (1969) who investigated a 12-year-old boy in whom a laparotomy for abdominal pain had revealed an intramural haematoma of the descending colon. It appears that this intramural bleeding may be spontaneous, or may follow trauma. In certain circumstances violent colicky contractions of the intestine may be sufficient to cause intramural bleeding as in case 2. The underlying fragility of tissue and bleeding diathesis undoubtedly predispose to these events.

Severe rectal bleeding from diverticula, or the friable intestinal wall is also an uncommon but serious hazard of the Ehlers-Danlos syndrome.

Jacobs (1957) reported a man with rectal bleeding, and he mentioned that the patient's affected brother had died from a massive rectal haemorrhage, which had followed an operation at which a friable inflamed bowel had been demonstrated. Lapayowker (1960) treated a man who presented with acute diverticulitis and who later had a laparotomy which revealed regional enteritis of the small bowel. The patient died after a postoperative period which was complicated by dehiscence of the wound, ileus, and rectal bleeding. Another individual, described by Green, Schuman, and Barron (1966), died after several operations for intractable colonic diverticulitis. This illness had been complicated by abscess and fistula formation, together with many episodes of rectal bleeding. It was suggested that the patient's illness might have been due to the inability of the tissues to localize the infection and produce a healthy granulation tissue. This particular patient also had a coagulation defect, which was described in detail by Kashiwagi, Riddle, Abraham, and Frame (1965).

Gastrointestinal bleeding may also take place in association with hiatus hernia and peptic ulceration. Grant and Aldor (1967) described two middle-aged sisters who both had a hiatus hernia and a peptic ulcer and several episodes of gastrointestinal haemorrhage. One sister underwent vagotomy and pyloroplasty, which was complicated by postoperative ileus and deep vein thrombosis.

Once bleeding occurs, it is made worse by the coagulation defect. However, the severity of the haemorrhagic diathesis is very variable, and its fundamental nature is obscure. Deficiency of plasma thromboplastin has been reported by Lisker, Nogueron, and Sanchez-Medal (1960), defects in platelet function were described by Goodman, Levitsky, and Friedman (1962), while Kashiwagi *et al* (1965) found abnormalities of platelet ultrastructure and aggregation. It is possible that the bleeding tendency is due to a combination of the coagulation defect, friable blood vessel walls, and abnormal perivascular connective tissue.

A patient with an acute abdomen due to a retroperitoneal haemorrhage was described by McKusick (1966). Necropsy revealed that the cause of the bleeding had been a dissection of the renal artery. Another woman died from a ruptured internal iliac artery, which had presented in the same way (Beighton, 1968). Arterial rupture of this type, involving large peripheral arteries, has previously been described by Mories (1960), McFarland and Fuller (1964), and by Lynch, Larsen, Wilson, and Magnuson (1965).

These serious complications of perforation and massive haemorrhage occur only in a minority of patients who may well have a clinically distinct form of the Ehlers-Danlos syndrome. However, even a routine operation may be made difficult by the fragility of tissue and the bleeding tendency. Sutures may tear out the tissues, and wound dehiscence may take place (Packer and Blades, 1954; Jacobs, 1957). The surgical management of the complications of the Ehlers-Danlos syndrome may present considerable technical problems (Beighton and Horan, 1969).

Eventration of the diaphragm has previously been observed by McKusick (1966) while Zalis and Roberts (1967) described a similar developmental defect in a young Negro. This patient's stomach passed through an opening and became strangulated in the thorax. Hiatus hernia has been reported by Brombart, Coupatez, and Laurent (1952), by McKusick (1966), by Grant and Aldor (1967), and by Papp and Paley (1966). The liability to this abnormality is readily explained on a basis of the laxity of the tissues.

There are reports of diverticula in almost every part of the gastrointestinal tract, and it is probable that these anomalies occur frequently. Gastric, duodenal, and colonic diverticula have been described by Brombart *et al* (1952) while Jacobs (1957) reported the presence of duodenal and colonic diverticulae in his patient. Dreyfus, Weill, Martineau, and Mathivat (1936) observed hyperelasticity of the mucous membranes and Brombart *et al* (1952) postulated that this factor could be responsible for the formation of diverticula and that it might cause prolapse of the gastric mucosa into the duodenum.

The liability to prolapse of the rectum may also be explained on a basis of the laxity of the tissues. Although this complication resolved during childhood in the patients in the series, it was still troublesome in middle age in the two sisters mentioned by Grant and Aldor (1967).

External herniae are very common in affected patients and they have been mentioned in case reports by many authors, including Katz and Steiner (1955) and Husebye and Getz (1958). Several of the patients in the series had operative repair, and in spite of the fragility of tissue the end result was usually satisfactory.

Other gastrointestinal features that have been demonstrated are visceroptosis (Ota and Yasuda, 1941) and gastric atony (Rossi and Angst, 1951), while megaoesophagus and megacolon were described by Mounier-Kuhn and Meyer (1943). Polycystic liver and kidneys were found at necropsy by Bannerman, Graf, and Upson (1967), and Rubinstein and Cohen (1964) reported a child who was presumably affected by the Ehlers-Danlos syndrome and who died from massive ectasia of the viscera through the abdominal wall. These findings

may well have been chance associations rather than true concomitants of the Ehlers-Danlos syndrome.

It appears that although structural abnormalities of the gastrointestinal tract are common findings in the Ehlers-Danlos syndrome, few patients have any serious complications. On the other hand, spontaneous perforation and massive haemorrhage are rare but dangerous hazards, while surgery may be made difficult by the bleeding tendency and the fragility of tissue.

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