

## EHLERS-DANLOS SYNDROME TYPE IV ASSOCIATED WITH ARTERIAL AND BOWEL PERFORATION

Alaa S. Abdul Jabbar, MBBS, ABIS

Ehlers-Danlos syndrome is a clinically, genetically and biochemically heterogeneous group of inherited connective tissue disorders.<sup>1</sup> The disorder was first described as early as 1682, but it was not until the early 1900s that the characteristic features of the syndrome were described by Ehlers and Danlos.<sup>2</sup> Ten types of Ehlers-Danlos syndrome have been described on the basis of clinical, genetic and/or biochemical differences.<sup>2</sup> It is now considered a heterogeneous group of disorders, the most lethal of which is type IV, which is also called the "arterial-ecchymotic" type.<sup>3</sup>

Ehlers-Danlos syndrome is characterized by hyperelasticity and fragility of the skin, hyperflexibility and looseness of the joints and a bleeding diathesis.<sup>4</sup> The eyes, gastrointestinal tract, bronchopulmonary tree, and cardiovascular system may also be affected by this defect in mesenchyme.<sup>4</sup> The incidence of Ehlers-Danlos syndrome is not known, but it is not rare. It is believed to be the most prevalent of the heritable disorders of connective tissue. It is most frequently seen in Caucasians of European origin and has a male predominance.<sup>4</sup> Most subjects have an autosomal dominant inheritance, and recessive inheritance is rare.<sup>6</sup> However, about 50% of cases represent new mutations,<sup>7</sup> and this was the case in our patient.

### Case Report

A 25-year-old female gravida 1, para 0, had a spontaneous normal vaginal delivery at 39 weeks' gestation after a normal antenatal period, and was discharged from hospital. A week later, she was hospitalized again with a sudden onset of severe abdominal pain. On examination, the patient was noted to be in shock. After resuscitation, urgent CT scan showed a large collection of retroperitoneal fluid, upon which intra-abdominal hemorrhage was diagnosed. At laparotomy, a massive hemoperitoneum and retroperitoneal hematoma were found. The source of the

Accepted for publication 26 August 2000. Received 22 December 1999.

bleeding was identified as a 1 cm tear in the left common iliac artery, which was oversewn. The patient received multiple units of packed red blood cells and fresh frozen plasma during the procedure. She was transferred to the Intensive Care Unit, where her condition improved.

One week later, the patient became septic with severe abdominal pain and was transferred again to the operating theater. Another laparotomy confirmed the presence of peritonitis and linear perforation of the right colon, for which right hemicolectomy was performed with end ileostomy in the right iliac fossa and transverse colonic mucous fistula in the left upper quadrant. The previous arterial repair was intact. One week later, a third laparotomy was done because of recurrent intra-abdominal sepsis with leaking of intestinal fluid through the abdominal wound. There were multiple small perforations in a segment of the jejunum. A 20 cm segment of jejunum was resected and the jejunum mucous fistula was fashioned in the upper part of the abdominal wound and end jejunostomy in the left iliac fossa. The patient's condition improved after the third operation, and she was transferred to the Intestinal Failure Unit, where a Hickman line was inserted and she was started on total parenteral nutrition (TPN). It was felt that the patient's condition was suggestive of Ehlers-Danlos syndrome type IV, and skin biopsy was sent for cell culture. A defect in type III collagen metabolism initially was not identified. However, on repeat examination, cultured skin fibroblasts were shown to produce a structurally abnormal type III collagen retained within the cells. The patient's clinical picture was consistent with the Ehlers-Danlos syndrome type IV. There was no family history of a similar problem and no previous similar attacks in the patient.

### Discussion

Ehlers-Danlos syndrome type IV is an often lethal disease caused by various mutations of type III collagen genes.<sup>8</sup> This type of collagen is particularly abundant in arterial walls, bowel wall, and the uterus.<sup>3</sup> First described by Barabas<sup>9</sup> as the arterial type, and Beighton<sup>10</sup> as the ecchymotic variant of Ehlers-Danlos syndrome, specific molecular abnormalities were first identified in 1975.<sup>11</sup>

---

From the Department of Surgery, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

Address reprint requests and correspondence to Dr. Abdul Jabbar: Department of Surgery, MBC-40, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Email: a\_abduljabbar@hotmail.com.

The clinical spectrum of Ehlers-Danlos syndrome type IV is wide. The disease can present with low birth weight, and subsequent failure to thrive, with small stature and low

weight. Joint dislocations and severe bruising with thin skin and capillary prominence or telangiectasia are common.<sup>8</sup> They include typical facial features (i.e., a thin, pinched nose and large eyes with a startling and prominent appearance, because of paucity of adipose tissue) and acrogeria (defining hands with fine fingers and covered by thin and wrinkled skin, which looks prematurely aged).<sup>7</sup> The association of both club foot and spontaneous pneumothorax with this syndrome has also been noted.<sup>6</sup>

The diagnosis of Ehlers-Danlos syndrome type IV is usually suspected in a patient with a combination of clinical manifestation and family history. It is confirmed only by culture of the patient's skin fibroblasts and demonstration of a defect in type III collagen metabolism,<sup>6</sup> a study that confirmed the diagnosis in our patient. Type I collagen metabolism was normal. Autio et al.<sup>5</sup> have reported noninvasive modern B-mode ultrasonic techniques to demonstrate thin skin, a characteristic of Ehlers-Danlos syndrome, in place of skin biopsy. The diagnosis and classification are confirmed by measuring type III and I amino terminal procollagen propeptide levels in skin interstitial fluid. The thickness and density of the skin, i.e., echogenicity, is studied by 30 MHz high-resolution ultrasonic device.

It is now well documented that patients with this disorder have increased vascular, surgical and anesthetic complications.<sup>2</sup> This syndrome carries a very high risk of lethal complications which appear to be enhanced by pregnancy.<sup>12</sup> Major complications of pregnancy can occur in the antenatal period, during labor and delivery, and postpartum, as was the case in our patient. Maternal mortality of up to 25% has been reported due to rupture of the artery, bowel and uterus.<sup>1</sup> The precise incidence of pregnancy complications in women with Ehlers-Danlos syndrome type IV is not really known, because usually only patients with complications are likely to be reported in the medical, genetic and obstetric literature.<sup>12</sup> The complications of pregnancy include rupture of the bowel, aorta, vena cava, or uterus, vaginal laceration, postpartum uterine hemorrhage, varicose veins, uterine and/or bladder prolapse, joint laxity, abdominal herniation, and wound dehiscence.<sup>1,2,12</sup> This has led some authors to recommend that patients with Ehlers-Danlos syndrome type IV should be advised against pregnancy,<sup>2</sup> or be counseled for early pregnancy termination.<sup>1,13</sup> If the patient opts for pregnancy, both she and her physician should at least be aware of the potential serious complications. Moreover, the patient should be given genetic counseling with regard to the risk of her offspring having the same severe form of the disease (there is a 50% chance of inheriting the syndrome).

The safest mode of delivery by a pregnant patient with Ehlers-Danlos syndrome is by elective cesarean section at (apparently) 36 weeks, with full vascular, surgical and intensive care cover.<sup>12</sup> The patient should be carefully monitored for several days postpartum, so that prompt intervention can be initiated in the event of vessel, bowel or uterine rupture.<sup>1</sup> Although Ehlers-Danlos syndrome type IV is rare, it carries a high risk of maternal morbidity and mortality, therefore, it is important to be aware of the diagnosis prior to pregnancy, and to have a high index of suspicion for arterial or viscous perforation in the face of acute abdominal findings.<sup>3</sup>

The hallmarks of the disease, however, are severe surgical complications, some of which are frequently fatal, and account for the reduced life expectancy of these patients, resulting in a mean age at death of 35 to 40 years.<sup>7,8</sup> These are spontaneous ruptures of aneurysms, arteriovenous fistulas or large-size arteries<sup>14</sup> (as occurred in our patient). Splenic rupture has also been reported.<sup>15</sup> Gastrointestinal complications include eventration of the diaphragm, diverticula, rectal prolapse, gastrointestinal bleeding and spontaneous perforation of the bowel.<sup>6,7</sup> Spontaneous bowel perforation is a rare but particularly troublesome complication because of its tendency to recur despite aggressive surgical management.<sup>6</sup> Bowel rupture typically happens in young adults and is usually situated in the sigmoid colon,<sup>6,7,16</sup> unlike our patient, who had perforation in the right colon and the small bowel.

Emergency surgery for acute bowel perforation in patients with Ehlers-Danlos syndrome should be carried out in the standard manner. Surgery in these patients has a high morbidity because of the extreme fragility of tissues, which is often described as tearing like "wet blotting paper." Sutures tend to tear them out, bowel walls are extremely friable and anastomosis is arduous. Small vessels are equally fragile, occasioning difficult hemostasis, oozing and hematoma formation.<sup>7,14</sup> Other notable surgical complications or difficulties are stenosis of anastomosis or stoma and tremendous intraperitoneal adhesion, which, when associated with intestinal fragility, frustrate the efforts of surgeons.<sup>6,7,16</sup>

Treatment of bowel perforation in these patients is controversial. Different surgical procedures have been advocated, but there is no large series study currently available to demonstrate the superiority of any one option. The simplest approach is to perform a classical Hartmann's procedure with a distal mucous fistula, or the construction of a Hartmann's pouch. It is widely accepted that there should be no anastomosis, as a permanent end colostomy/ileostomy greatly reduces the risk of recurrence.<sup>6,7,16</sup>

The reported experience, although small, suggests that restoration of bowel continuity is associated with a high incidence of recurrent perforation, and that permanent colostomy/ileostomy status is advisable, despite the young ages of most of the patients.<sup>16</sup> Unless a life-saving

procedure is needed, it is believed that laparotomy should be avoided at all costs in these patients.

In case of a spontaneous bowel rupture in a young adult without any obvious cause at laparotomy such as diverticulitis, neoplasia, Crohn's disease, or infectious or ischemic colitis, and in the absence of corticosteroid therapy, the possibility of Ehlers-Danlos syndrome type IV should be considered.<sup>7</sup> Thorough personal and family medical history and clinical examination should be obtained, and one should look for typical signs and symptoms of the disease and, if found, skin fibroblasts culture should be performed to establish a definitive diagnosis.<sup>7</sup>

### Acknowledgements

The author is grateful to Ms. Raquel Glorioso-Rivera for editing this manuscript.

### References

- Rudd NL, Holbrook KA, Nimrod C, Byers PH. Pregnancy complications in type IV Ehlers-Danlos syndrome. *Lancet* 1983;1:50-3.
- Snyder RR, Gilstrap LC, Hauth JC. Ehlers-Danlos syndrome and pregnancy: case report. *Obstet Gynecol* 1983;61:649-51.
- Brees CK, Gall SA. Rupture of the external iliac artery during pregnancy: a case of type IV Ehlers-Danlos syndrome. *J Ky Med Assoc* 1995;93:553-5.
- Ainsworth SR, Aulicino PL. A survey of patients with Ehlers-Danlos syndrome. *Clin Orthop* 1993;286:250-6.
- Autio P, Turpeinen M, Risteli J, Kallioinen M, Kiistala U, Oikarinen A. Ehlers-Danlos type IV: non-invasive techniques as diagnostic support. *Br J Dermatol* 1997;137:653-5.
- Stillman AE, Painter R, Hollister W. Ehlers-Danlos syndrome type IV: diagnosis and therapy of associated bowel perforation. *Am J Gastroenterol* 1991;86:360-2.
- Berney T, Scala GL, Vettovel D, Gumowski D, Hauser C, Frileux P, et al. Surgical pitfalls in a patient with type IV Ehlers-Danlos syndrome and spontaneous colonic rupture. *Dis Colon Rectum* 1994;37:1038-42.
- Pope FM, Narcisi P, Nicholls AC, Liberman M, Oorthuys JWE. Clinical presentation of Ehlers-Danlos syndrome type IV. *Arch Dis Child* 1988;63:1016-25.
- Barabas A. Vascular complications with Ehlers-Danlos syndrome with special reference to the "arterial type" of Sack's syndrome. *J Cardiovasc Surg (Torino)* 1972;13:160-7.
- Beighton P. *The Ehlers-Danlos syndrome*. London: William Heinemann Medical Books, 1970.
- Pope FM, Martin GR, Lichtenstein JR, et al. Patients with Ehlers-Danlos syndrome lack type III collagen. *Proc Natl Acad Sci USA* 1975;72:1314-6.
- Wood J. Case study: pregnancy and Ehlers-Danlos syndrome type IV. *Midwives Chron* 1993;108:446-8.
- Peaceman AM, Cruikshank DP. Ehlers-Danlos syndrome and pregnancy: association of type IV disease with maternal death. *Obstet Gynecol* 1987;69:428-31.
- Soucy P, Eidus L, Keeley F. Perforation of the colon in a 15-year-old girl with Ehlers-Danlos syndrome type IV. *J Pediatr Surg* 1990;25:1180-2.
- Harris SC, Slater DN, Austin CA. Fatal splenic rupture in Ehlers-Danlos syndrome. *Postgrad Med J* 1985;61:259-60.
- Sykes EM. Colon perforation in Ehlers-Danlos syndrome: report of two cases and review of the literature. *Am J Surg* 1984;147:410-3.