

[CASE REPORT]

Mobile Cecum in a Young Woman with Ehlers-Danlos Syndrome Hypermobility type: A Case Report and Review of the Literature

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Abstract:

Ehlers-Danlos syndrome, hypermobility type (EDS-HT) is unexpectedly common and is associated with a high rate of gastrointestinal manifestations. We herein report the first documented case of mobile cecum associated with EDS-HT. A 21-year-old woman with repeated right lower abdominal pain was initially diagnosed with EDS-HT. Abdominal examinations performed in the supine position, such as CT and ultrasonography, showed no gross abnormalities. In contrast, oral barium gastrointestinal transit X-ray images obtained with changes in the patient's body position revealed position-dependent cecal volvulus with mobile cecum. She was finally discharged with a dramatic resolution of her symptoms after laparoscopic cecopexy for mobile cecum.

Key words: Ehlers-Danlos syndrome hypermobility type (EDS-HT), mobile cecum, ptosis, laparoscopic cecopexy, postural tachycardia syndrome, cecal volvulus

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Introduction

Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous group of hereditary connective tissue disorders that is characterized by articular hypermobility, skin extensibility, and connective tissue fragility. The Villefranche classification, adopted in 1998, defines six major subtypes of EDS based on the relative degree of involvement of the skin, skeleton, joints, and vasculature: the classical, hypermobility, vascular, kyphoscoliosis, arthrochalasia, and dermatosparaxis types. The overall frequency of EDS has been estimated to be 1 in 5,000. EDS, hypermobility type (EDS-HT), which is currently recognized as the most common form, mainly manifests as generalized joint hypermobility without obvious skin problems (1-4). Joint hyper-

mobility syndrome (JHS) is a similar condition to EDS-HT and discriminating between the two can be quite difficult due to the lack of delineating characteristics (5). In fact, EDS-HT is diagnosed clinically based on the current classification (1, 2) whereas JHS is diagnosed according to the revised Brighton criteria (6). Based on a literature review that was performed in this report, JHS appears to be the same clinical entity as EDS-HT. Although EDS-HT is mostly transmitted in an autosomal dominant pattern, the details of the associated genetic defect remain unknown; moreover, a small number of EDS-HT patients exhibit tenascin-X deficiency, a rare condition caused by an autosomal recessive mutation of the *TNXB* gene (7, 8). In recent years, an increasing number of studies have suggested that functional digestive symptoms, namely irritable bowel syndrome, gastroesophageal reflux disease, and constipation are common

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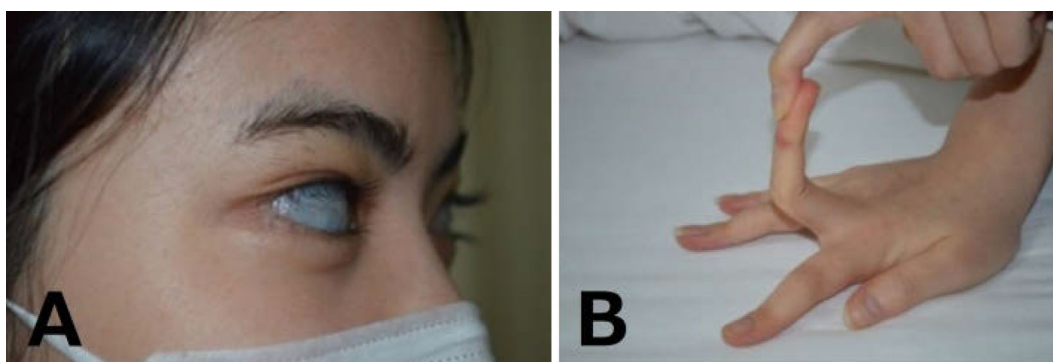


Figure 1. Physical findings. (A) Blue sclera, (B) hypermobile joint of the right middle finger.

complications in patients with EDS-HT (9-12). Although information concerning the etiology of the abdominal symptoms in EDS-HT is still lacking, several reports have suggested that visceral ptosis is a possible cause (13, 14).

Mobile cecum is defined as the abnormal mobility of the cecum and ascending colon, which are not attached to the lateral or posterior peritoneal wall. This abnormality is thought to be the result of the failure of the right colonic mesentery to fuse with the lateral and posterior peritoneum during the embryological period (15, 16). An autopsy series estimated that the incidence of mobile cecum in the general population was 11.2% (17). Patients with mobile cecum present with chronic right lower quadrant abdominal pain, similar to the present patient. Laparoscopic cecopexy is probably the optimal strategy to treat mobile cecum syndrome (18).

To the best of our knowledge, there are no previous reports on the link between mobile cecum and EDS-HT. Our patient presented with long-standing gastrointestinal symptoms of unknown etiology. From the time of the patient's first visit to our hospital, it took more than three months to reach the final diagnosis of mobile cecum associated with EDS-HT. We herein demonstrate the detailed diagnostic process.

Case Report

A 21-year-old single Japanese woman was admitted to the department of gastroenterology in our hospital with a 10-month history of repeated colicky right lower abdominal pain, bloating, vomiting, and body weight loss (8 kg) due to difficulty in eating. The patient had visited the emergency department of our hospital several times in the month prior to her admission. Despite the lack of sufficient evidence to make a definitive diagnosis, she was initially treated with a single oral dose of azithromycin (1 g) for the suspected pelvic inflammatory syndrome, and was subsequently treated with a 7-day course of intravenous cefmetazole (3 g daily) for suspected chronic appendicitis. However, her symptoms persisted.

Although there were no notable episodes of illness in her childhood, she started to suffer from minor episodes of general fatigue, night sweats, and palmar hyperhidrosis during

early adolescence. Furthermore, she had tended to experience moderate orthostatic symptoms such as nausea, headache, back pain, and dizziness in the past few years. However, she had never undergone a detailed evaluation until admission.

A physical examination on admission revealed that she was 153 cm tall and that her weight was 46 kg (body mass index=19.7). Her abdomen was soft, and mild tenderness was present in the right lower quadrant of the abdomen. She reported that her abdominal symptoms were relieved by adopting a right lateral decubitus position. The Patient's laboratory data including her blood cell counts, inflammatory marker levels, and her liver, kidney, thyroid and adrenal cortex functions were within the normal limits. The findings of abdominal ultrasonography, contrast-enhanced computed tomography, and upper and lower gastrointestinal endoscopy were unremarkable. Thus, our tentative diagnosis at the time of admission was either functional gastrointestinal disorder or psychosomatic disease.

During the first three months after admission, she underwent conservative treatment with an oral anti-cholinergic agent (scopolamine, 10 mg, three times a day), an oral tricyclic anti-depressant (amitriptyline, 10 mg, three times a day), and occasional bowel resting with intravenous rehydration. Despite the treatment, her symptoms remained unchanged. Accordingly, it was necessary to reassess her condition and we performed a careful re-examination. As a result, we identified several previously overlooked physical findings: blue sclera (Fig. 1A), finger joint hypermobility (Fig. 1B), flat feet, and hallux valgus. With the exception of blue sclera, there was no evidence of scoliosis, skin, echocardiographic, or ophthalmologic abnormalities. An additional assessment of joint hyperextensibility according to the Beighton hypermobility scale was positive with a score of 5/9 (Table 1). Moreover, an orthostatic tolerance test showed apparent postural tachycardia (Fig. 2). At this point, we began to suspect that EDS-HT was her underlying condition. Further questioning revealed that her family history was highly suggestive of EDS-HT. Although none of her family members had been diagnosed with EDS-HT, her brother and sister had marked joint hypermobility. Her paternal aunt also had a history of repeated sub-luxation of the shoulder. How-

Table 1. The Beighton Hypermobility Scale.

one point for each hand
1) passive dorsiflexion of the fifth finger beyond 90 degrees
2) passive apposition of the thumb to the flexor aspect of the forearm
3) hyperextension of the elbows beyond 10 degrees
4) hyperextension of the knees beyond 180 degrees
one point
5) forward flexion of waist with palms on the floor
A score of 5/9 or greater is considered an indication of generalized joint hypermobility. In this case, she met the following criteria of 1), 2), and 5).

ever, she was the only member of her family to experience episodes of postural tachycardia, blue sclera, and unexplained gastrointestinal symptoms. Finally, we made a definitive diagnosis of EDS-HT according to the current classification of EDS (Table 2). She subsequently underwent a gastrointestinal transit X-ray study with oral barium to identify gastrointestinal ptosis related to EDS. There were no abnormalities of the stomach, duodenum, or small intestine, but the cecum was shifted medially with 180 degrees of torsion in the upright position (Fig. 3A). In the subsequent supine image, the entire colon was unexpectedly found to be in a normal anatomical position. Moreover, the cecum and ascending colon dropped toward the pelvic cavity when she changed from an upright position to the supine position on the fluoroscopic table (Fig. 3B, C). We therefore concluded that intermittent cecal volvulus caused by mobile cecum had contributed to her abdominal symptoms.

At four months after admission, she finally underwent transumbilical single-incision laparoscopic appendectomy and cecopexy. The intraoperative findings revealed that the cecum and ascending colon were entirely unattached to the retroperitoneal wall and were free to rotate. There was no evidence of mesenterium commune. Appendectomy could be performed extracorporeally through the umbilicus due to the mobility of the ileocecal region. The cecum and ascending colon were fixed to the lateral peritoneal wall with interrupted absorbable sutures. There was no pathological evidence of appendicitis. Her abdominal symptoms dramatically improved soon after the surgery and she has remained free of recurrence over a 2-year follow-up period. The surgical skin wound healed normally. Although her orthostatic symptoms remained unchanged after surgery, they were effectively treated with oral propranolol (20 mg, three times daily).

Discussion

The different types of EDS are distinguished based on specific symptoms, genetic differences, and the pattern of inheritance (Table 2) (1, 2). A diagnosis of EDS is generally suspected when a clinical examination reveals abnormal connective tissue manifestations, commonly joint hypermo-

bility. The Beighton hypermobility scale, shown in Table 1, is widely accepted for the evaluation of joint hypermobility (19). Patients with EDS-HT develop various extra-articular manifestations, ranging from asymptomatic to severe. Orthostatic intolerance, including postural orthostatic tachycardia syndrome (POTS), and gastrointestinal symptoms are also indicated as representative extra-articular manifestations (20, 21). POTS, which mainly affects young women under 40 years of age, is a heterogeneous disorder characterized by sustained excessive heart rate elevation (≥ 30 beats per minute) without hypotension upon standing (22, 23). The most striking symptomatic manifestation is orthostatic intolerance due to headache, lightheadedness, and palpitations. Low-dose oral propranolol therapy is very effective for reducing the symptoms and orthostatic tachycardia in EDS-HT patients with POTS (24, 25). The present case showed the major characteristic features of EDS-HT, including a family history, joint hypermobility, gastrointestinal symptoms, and orthostatic tachycardia. Additionally, no pathogenic variants were detected through next generation sequencing-based genetic screening of the 17 genes responsible for hereditary connective tissue disorders: *FBN1* (Marfan syndrome); *FBN2* (Beals syndrome); *TGFBR1*, *TGFBR2* (Loeys-Dietz syndrome); *COL5A1*, *COL5A2* (EDS, classical type); *TNXB* (EDS, hypermobility type found in a small number of patients); *COL3A1* (EDS, vascular type); *PLOD1* (EDS, kyphoscoliosis type); *COL1A1*, *COL1A2* (EDS, arthrochalasia type); *ADAMTS2* (EDS, dermatosparaxis type); *CHST14* (EDS, musculocontractural type); *ZNF469* (Brittle cornea syndrome); *FKBP14* (EDS with progressive kyphoscoliosis, myopathy, and hearing loss); *SLC39A13* (EDS-like spondylocheirodysplasia); and *B4GALT7* (EDS, progeroid type). This case report raises several clinical implications.

First, patients with unexplained gastrointestinal symptoms, if non-fatal and long-standing, are often simply diagnosed with functional gastrointestinal disorder or psychosomatic disease (as in the present case). Without suitable management, there might be a long-term impact on their quality of life. Although nearly 4 months was required, we fortunately detected cecal volvulus with mobile cecum when we attempted to confirm the presence of gastrointestinal tract ptosis associated with EDS-HT. More importantly, the strong link between abdominal symptoms and EDS-HT is not well known by most clinicians. Given the high prevalence of EDS-HT, there might be many patients with EDS-HT in whom unexplained gastrointestinal symptoms are ignored. We should consider the possibility of EDS-HT at least once when we encounter patients with unexplained gastrointestinal symptoms.

Second, several factors were associated with the delay in the final diagnosis. On the gastrointestinal X-ray study with oral barium, the mobile cecum with right-sided colon ptosis was gravity-dependent and thus appeared in an anatomically normal location when the patient was in the supine position. Moreover, the cecal volvulus, which was complicated by

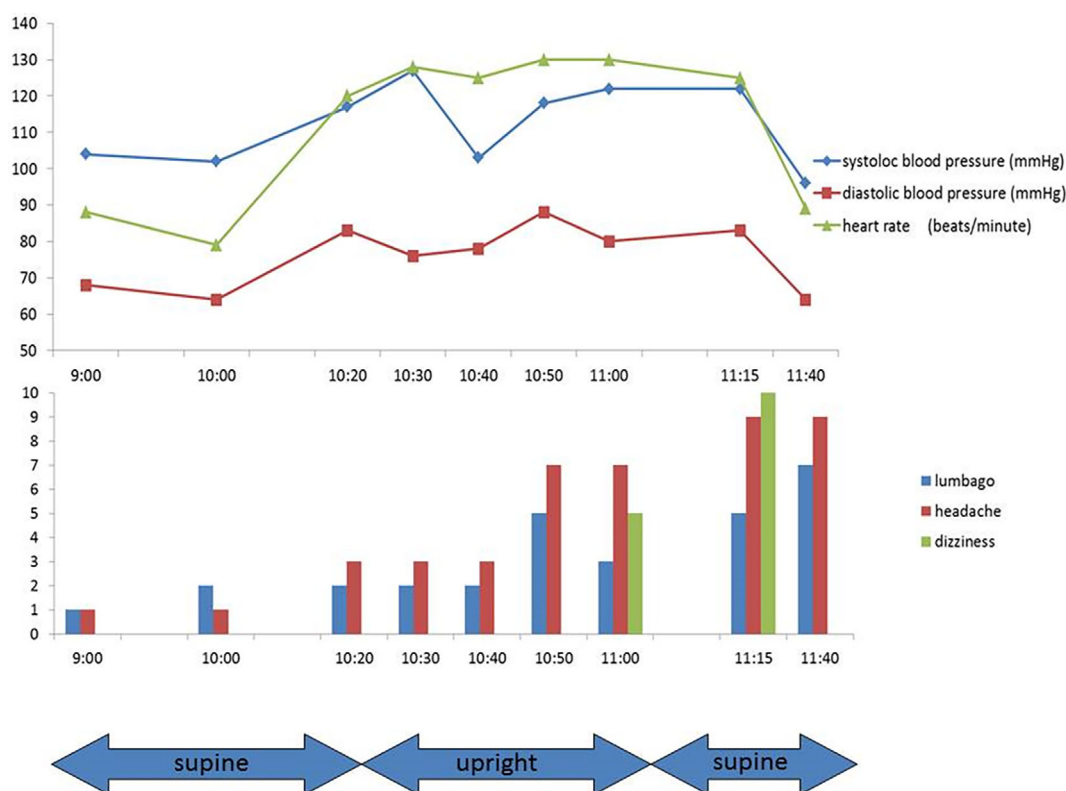


Figure 2. The results of an orthostatic tolerance test that was performed in the morning. The horizontal axis represents the time course. The upper panel shows a >30 beat per minute increase in her heart rate without hypotension soon after changing from the supine position to an upright position. This increased heart rate was sustained until she lay down. The lower panel shows the burden of symptoms, including lumbago, headache, and dizziness, which was assessed using subjective symptom rating scales. The symptoms were scored from 0 to 10, with higher scores reflecting worse subjective symptoms. Her symptom scores increased markedly after changing to an upright position.

Table 2. Current Classification of Ehlers-Danlos Syndromes.

Descriptive	Clinical features	Genes	Inheritance
Classical	Marked joint hypermobility, skin hyperextensibility, bruising, abnormal scarring	<i>COL5A1</i> , <i>COL5A2</i>	AD
Hypermobility	Marked joint hypermobility, minor skin findings	Largely unknown, <i>TNXB</i>	AD
Vascular	Thin translucent skin, marked bruising, small joint hypermobility, high risk for rupture of arteries, bowel and gravid uterus	<i>COL3A1</i>	AD
Kyphoscoliosis	Kyphoscoliosis recalcitrant to surgery, joint hypermobility, risk for arterial rupture, ocular fragility	<i>PLOD1</i>	AR
Arthrochalasia	Marked joint hypermobility, bilateral congenital hip dislocation	<i>COL1A1</i> , <i>COL1A2</i>	AD
Dermatosparaxis	Soft, fragile skin with late onset skin redundancy, blue sclerae, joint hypermobility	<i>ADAMTS2</i>	AR

AD: autosomal dominant fashion, AR: autosomal recessive fashion

mobile cecum, and which probably contributed directly to the abdominal symptoms, occurred intermittently and reversibly without strangulation. Routine abdominal imaging examinations such as CT and ultrasonography are usually performed with the patient in the supine position. Thus, in the present case, no gross abnormalities were observed. In fact, the patient had undergone such examinations several times

while suffering from abdominal symptoms. However, no signs indicating the torsion, obstruction or ischemia of alimentary tract were detected. Our case suggests that confirming the anatomical changes of the gastrointestinal tract in several body positions can be a clue that may lead to an early diagnosis of mobile cecum. An X-ray study with oral barium would seem to be the preferred approach. Although

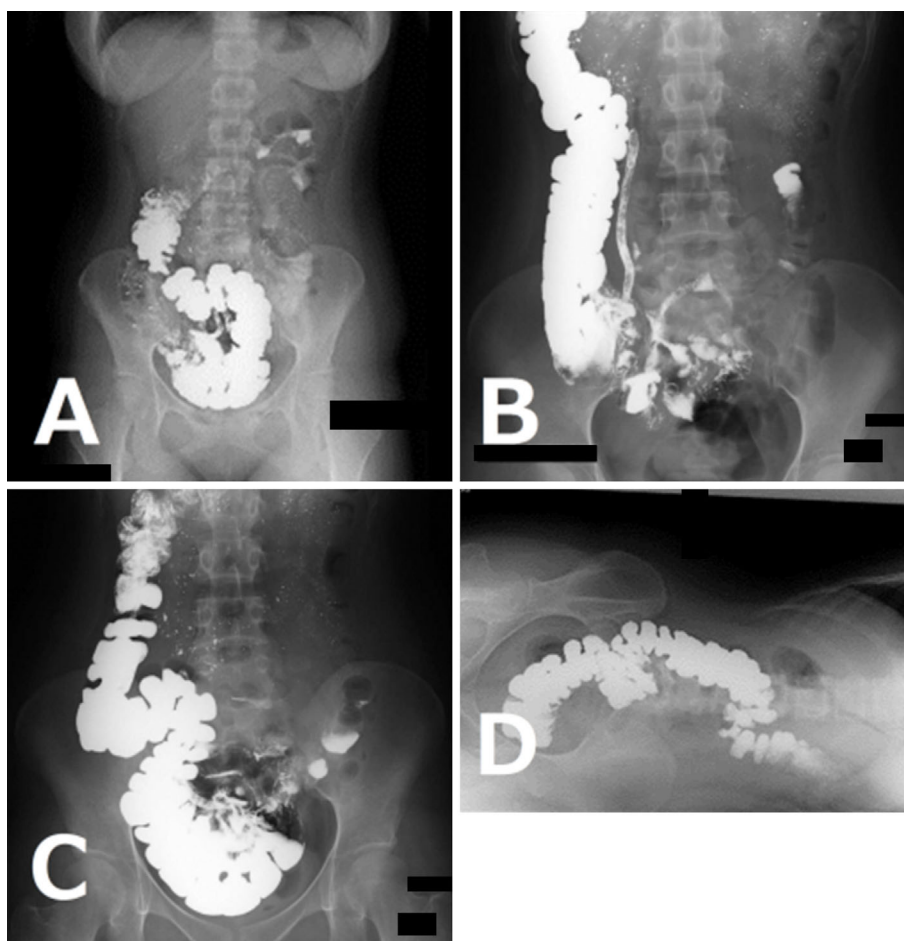


Figure 3. Gastrointestinal transit X-ray study with oral barium. (A) The upright image obtained 3 hours after the oral administration of barium shows the cecum displaced medially with 180 degrees of torsion. (B) The supine image shows the cecum and ascending colon located in a normal anatomical position. (C) The image shows the cecum and ascending colon displaced toward the pelvic cavity when the patient changed from the supine position to the upright position on the fluoroscopic table. (D) A left lateral decubitus image showing that the entire right sided colon dropped medially beyond the vertebral line.

it is difficult to currently elucidate whether mobile cecum occurs alone or in connection with EDS-HT, gastrointestinal tract ptosis has been reported as a possible cause of abdominal symptoms in patients with EDS-HT (13, 14). We should also pay more attention to mobile cecum as one of the phenotypes of ptosis. The accumulation of further case reports on the relationship between mobile cecum syndrome and EDS-HT is awaited.

Third, the patient's abdominal symptoms resolved completely following laparoscopic cecopexy for mobile cecum. However, the long-term postoperative prognosis of mobile cecum in patients treated by laparoscopic cecopexy remains unknown. In addition, previous reports of surgical attempts to correct visceral ptosis in patients with EDS-HT suggested that surgery was ineffective due to a high rate of relapse. Reinstein et al. described a case of small bowel ptosis and elongated transverse colon ptosis (13). Dordoni et al. also reported a case of multiple synchronous visceral ptosis that affected the kidneys, stomach, liver, ovaries and heart, and

hypothesized that a loose visceral ligament might contribute to the pathophysiology of ptosis (14). In our case, it is clear that the patient's mobile cecum was attributable to the absence of the mesenteric ligament along with right-sided colon. However, it is uncertain whether the patient had a loose visceral ligament. Thus, subsequent follow-up is necessary because there are concerns about the sympatric and heterotopic recurrence of visceral ptosis.

Finally, overt extra-articular symptoms, such as POTS and abdominal symptoms, rather than occult joint hypermobility could be important indicators for EDS-HT, as they were in this case. Because these extra-articular manifestations are not included in the diagnostic criteria for EDS-HT, clinicians must recognize the whole aspect of EDS-HT in the real clinical setting. However, it is unclear why blue sclera, which are absent in ordinary EDS-HT, were observed only in this patient among all of her family members.

In conclusion, we described a rare case of mobile cecum in an EDS-HT patient with gastrointestinal symptoms. This

report shows that gastrointestinal symptoms related to EDS-HT could be found in a patient suffering from long-standing abdominal symptoms of unidentified etiology.

The authors state that they have no Conflict of Interest (COI).

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References

- Beighton P, De Paepe A, Steinmann B, et al. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet* **77**: 31-37, 1998.
- Byers PH, Murray ML. Ehlers-Danlos syndrome: a showcase of conditions that lead to understanding matrix biology. *Matrix Biol* **33**: 10-15, 2014.
- Steinmann B, Royce PM, Superti-Furga A. The Ehlers-Danlos syndrome. In: *Connective Tissue and Its Heritable Disorders*. Royce PM, Steinmann B, Eds. Wiley-Liss, New York, NY, USA, 2002: 431-524.
- De Paepe A, Malfait F. The Ehlers-Danlos syndrome. A disorder with many faces. *Clin Genet* **82**: 1-11, 2012.
- Tinkle BT, Bird HA, Grahame R, et al. The lack of clinical distinction between the hypermobility type of Ehlers-Danlos syndrome and the joint hypermobility syndrome (a.k.a hyper mobility syndrome). *Am J Med Genet A* **149A**: 2368-2370, 2009.
- Grahame R, Bird HA, Child A. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). *J Rheumatol* **27**: 1777-1779, 2000.
- Schalkwijk J, Zweers MC, Steijlen PM, et al. A recessive form of the Ehlers-Danlos syndrome caused by tenascin-X deficiency. *N Engl J Med* **345**: 1167-1175, 2001.
- Burch GH, Gong Y, Liu W, et al. Tenascin-X deficiency is associated with Ehlers-Danlos syndrome. *Nature Genetics* **17**: 104-108, 1997.
- Castori M, Sperduti I, Celletti C, et al. Symptom and joint mobility progression in the joint hypermobility syndrome (Ehlers-Danlos syndrome, hypermobility type). *Clin Exp Rheumatol* **29**: 998-1005, 2011.
- Zeitoun JD, Lefevre JH, de Parades V, et al. Functional digestive symptoms and quality of life in patients with Ehlers-Danlos syndromes: results of a national cohort study on 134 patients. *PLoS One* **8**: e80321, 2013.
- Fikree A, Grahame R, Aktar R, et al. A prospective evaluation of undiagnosed joint hypermobility syndrome in patients with gastrointestinal symptoms. *Clin Gastroenterol Hepatol* **12**: 1680-1687, 2014.
- Nelson AD, Mouchli MA, Valentin N, et al. Ehlers Danlos syndrome and gastrointestinal manifestations: a 20-year experience at Mayo Clinic. *Neurogastroenterol Motil* **27**: 1657-1666, 2015.
- Reinstein E, Pimentel M, Pariani M, et al. Visceroptosis of the bowel in the hypermobility type of Ehlers-Danlos syndrome: presentation of a rare manifestation and review of literature. *Eur J Med Genet* **55**: 548-551, 2012.
- Dordoni C, Ritelli M, Venturini M, et al. Recurring and generalized visceroptosis in Ehlers-Danlos syndrome hypermobility type. *Am J Med Genet A* **161**: 1143-1147, 2013.
- Printen KJ. Mobile cecum syndrome in the adult. *Am Surg* **42**: 204-205, 1976.
- Rogers RL, Harford FJ. Mobile cecum syndrome. *Dis Colon Rectum* **27**: 399-402, 1984.
- Wolfer JA, Beato LE, Anson BJ. Volvulus of the cecum. Anatomical factors in its etiology: report of a case. *Surg Gynecol Obstet* **74**: 882-894, 1942.
- Tsushimi T, Kurazumi H, Takemoto Y, et al. Laparoscopic cecopexy for mobile cecum syndrome manifesting as cecal volvulus: report of a case. *Surg Today* **38**: 359-362, 2008.
- Beighton P, Solomon L, Soskolne CL. Articular mobility in an African population. *Ann Rheum Dis* **32**: 413-418, 1973.
- Mathias CJ, Low DA, Iodice V, et al. Postural tachycardia syndrome-current experience and concepts. *Nat Rev Neurol* **8**: 22-34, 2012.
- Rowe PC, Barron DF, Calkins H, et al. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J Pediatr* **135**: 494-499, 1999.
- Thieben MJ, Sandroni P, Sletten DM, et al. Postural orthostatic tachycardia syndrome: the Mayo clinic experience. *Mayo Clin Proc* **82**: 308-313, 2007.
- Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neutrally mediated syncope and the postural tachycardia syndrome. *Auton Neurosci* **161**: 46-48, 2011.
- Arnold AC, Okamoto LE, Diedrich A, et al. Low-dose propranolol and exercise capacity in postural tachycardia syndrome: a randomized study. *Neurology* **80**: 1927-1933, 2013.
- Raj SR, Black BK, Biaggioni I, et al. Propranolol decreases tachycardia and improves symptoms in the postural tachycardia syndrome: less is more. *Circulation* **120**: 725-734, 2009.

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