Radiology Case Reports

Volume 3, Issue 2, 2008

Ehlers-Danlos Syndrome Presenting as Severe Headache in a Young Adult

Sara R. Alcorn, Marie-Adele Sorel, Stephan Auerbach, M.D., and Kitt Shaffer, M.D., Ph.D.

A 27-year-old male with a positive family history of abdominal aortic aneurysm presented to his primary care physician and ultimately to the emergency department with the worst headache of his life and hypertension. An aneurysm of the right internal carotid artery was noted on CT and MRI. Upon further imaging and analysis, multiple vascular abnormalities were found, including possible dissection or pseudoaneurysm and multifocal narrowing and dilatation of the arteries of the head and neck. The patient underwent genetic testing revealing Ehlers-Danlos, type IV.

Case Report

A 27-year-old man presented to the emergency department complaining of one week of severe headache and neck pain. The headache was an intermittent, stabbing pain localized to the left occiput. This intermittent pain was superimposed on a constant, dull, left-sided headache and neck pain. The onset of head and neck pain occurred while the patient was working at a computer. He denied antecedent strenuous activity or Valsalva maneuver. The pain was only partially reduced by applying pressure to the area and by taking over-the-counter acetaminophen/aspirin/caffeine (Excedrin) analgesics. The patient denied fever, nasal congestion, nausea, vomiting, photophobia, numbness, weakness, or previous history of headaches. The patient smoked tobacco but denied current alcohol or illicit drug use. His past medical history was unremarkable. Family history was notable for a father with hypertension who died at age 47 due to a ruptured abdominal aortic aneurysm.

On physical exam, the patient was afebrile, with normal heart rate, blood pressure of 159/127 mm Hg, and normal respiratory rate and oxygen saturation. His height was 5 feet 8 inches with a body mass index of 20.83 kg/m2. Head and neck exam was normal. There was no temporal artery tenderness or meningismus. Palpation elicited reproducible pain at the left occipital insertion of the trapezius. The skin was warm and dry, with no rash, laxity, or noted thinning. His cardiac, pulmonary, and abdominal exams were unremarkable. His neurological exam revealed clear and fluent speech, intact cranial nerves II-XII, 5/5 strength throughout, and intact sensation. Gait was normal, and there was no nystagmus. He was alert and oriented. Laboratory inves-

Citation: Alcorn SR, Sorel M-A, Auerbach S, Shaffer K. Ehlers-Danlos syndrome presenting as severe headache in a young adult. Radiology Case Reports. [Online] 2008;3:172.

Abbreviations: CT, computed tomography; CTA, computed tomographic angiography; MRA, Magnetic resonance angiography; MRI, magnetic resonance imaging

Sara R. Alcorn (Email: Sara_Alcorn@hms.harvard.edu), and Marie-Adele Sorel (Email: Marie-Adele_Sorel@hms.harvard.edu) are at Harvard Medical School, Boston, USA.

Stephan Auerbach, M.D., and Kitt Shaffer, M.D., Ph.D., are in the Department of Radiology, Harvard Medical School and Cambridge Health Alliance, Cambridge, MA, USA.

Published: April 21, 2008

DOI: 10.2484/rcr.v3i2.172

tigations revealed complete blood count and chemistries within normal limits.

The patient was given hydromorphone and clonidine, which improved the pain and reduced his blood pressure to 140/94 mm Hg. The patient followed up with his primary care physician four days after initial presentation, and was sent back to the emergency department due to persistent pain and hypertension. In the emergency department, the patient reported no improvement in his symptoms. He continued to deny additional constitutional, neurological, cardiovascular, or gastrointestional symptoms.

On repeat physical exam, the patient was afebrile, with normal heart rate, blood pressure of 167/115 mm Hg, and normal respiratory rate and oxygen saturation. There were otherwise no changes to the exam from four days prior. Laboratory assessment of complete blood count, basic metabolic profile, thyroid stimulating hormone, and free thyroxine (T4) were within normal limits. Serum and urine toxicology screens were negative. The patient was admitted for further evaluation and management of his headache and hypertension. He was started on captopril and verapamil for hypertension and butalbital/acetaminophen/caffeine (Fioricet) for headache.

The patient underwent a head CT with contrast, which showed a vascular abnormality involving the right carotid artery (Fig. 1). Brain MRI showed unremarkable brain parenchyma and identified an abnormality of the high cervical right internal carotid artery (Fig. 2). The artery was patent, but dilated, with a surrounding contour abnormality with intermediate signal consistent with a saccular aneurysm, pseudoaneurysm or possibly a carotid body tumor. MRA was also performed, confirming aneurysm of the right internal carotid artery. The studies also depicted an abnormal segment of the distal left vertebral artery containing subacute thrombus. On the same day, the patient underwent CT angiography of the neck. This study corroborated the finding of saccular dilatation of the right internal carotid artery approximately six centimeters cephalad to the bifurcation, with thrombosis surrounding the patent lumen consistent with a partially thrombosed aneurysm or pseuodaneurysm. An additional neck CT with contrast demon-

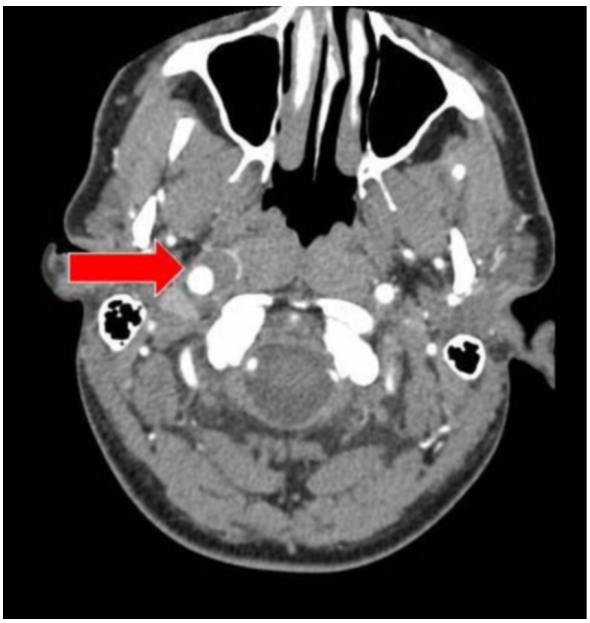

Figure 1. 27-year-old man with Ehlers-Danlos syndrome, type IV. Axial CT with contrast of the head, highlighting dilated right internal carotid artery with a surrounding crescent of soft tissue density.

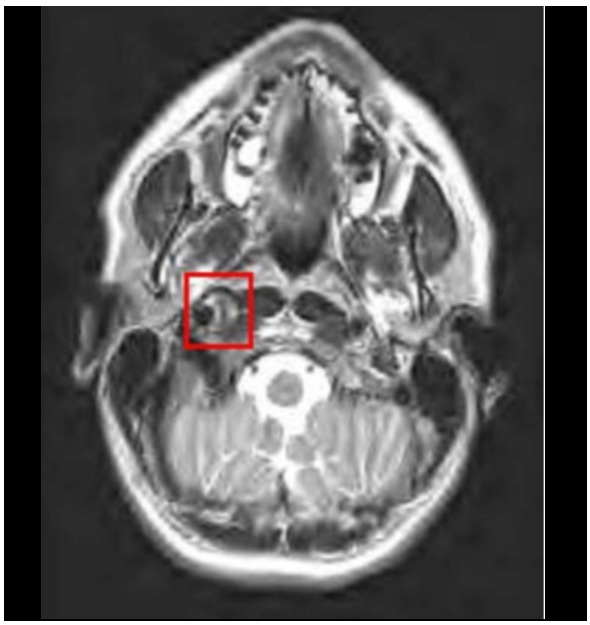

Figure 2. Axial magnetic resonance T2 image of the head, highlighting dilated right internal carotid artery with a surrounding crescent of intermediate signal.

DOI: 10.2484/rcr.2008.v3i2.172

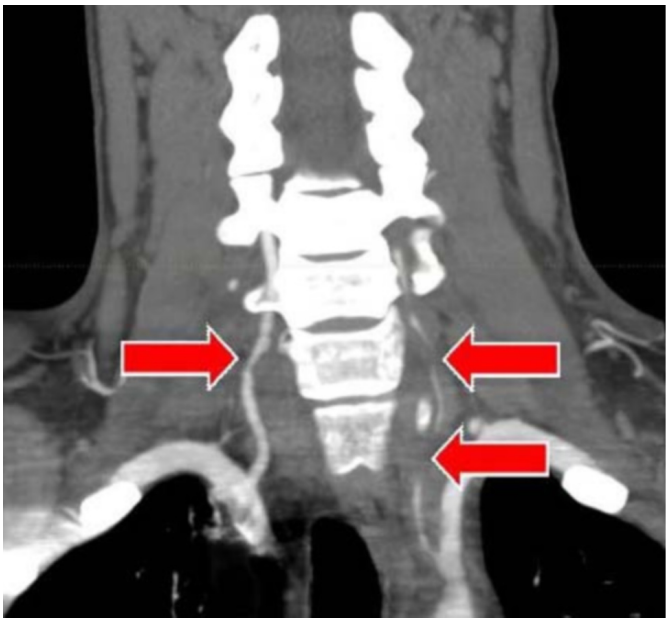

Figure 3. Coronal CT with contrast, demonstrating multiple sites of stenosis in left and right vertebral arteries.

strated several areas of narrowing and dilatation of the left vertebral artery (Fig. 3). At least one of the stenotic left vertebral artery segments appeared to be a chronic dissection, with a crescentic rim of thrombus surrounding the narrowed patent lumen. Additionally, there was an isolated area of stenosis of the right vertebral artery with post-stenotic dilatation (Figs. 3-4). The patient also underwent a chest CT, which demonstrated an abnormality of the left subclavian artery, with a crescentic rim of soft tissue tracking with the vessel, beginning at its origin (Figs. 5-6). As in the left vertebral artery, the crescentic morphology favored a thrombosed dissection over other possibilities such as mural inflammation from vasculitis or fibromuscular dysplasia.

Lumbar puncture was performed and revealed high protein, 100 lymphocytes, and 160 red blood cells, with slight xanthochromia, consistent with intracranial bleed. Serum investigations for erythrocyte sedimentation rate (ESR), C-reactive protein, rheumatoid factor, antinuclear antibody (ANA), and c-,p-, and x-anti-neutrophil cytoplasmic antibodies were negative. Aldosterone was elevated at 21 (reference range 1-16) and renin was 4.23. Renal ultrasound showed nonspecific cortical thinning without signs of hydronephrosis or calculi.

The patient was transferred to a tertiary care hospital for neurosurgery consultation. There, laboratory investigations revealed C-reactive protein elevated at 21.8 (reference range <8.0) and thyroglobulin mildly elevated at 44.6 (reference range 4.0-40.0). Although rheumatoid factor remained negative, ANA was found to be positive at 1:40 but negative at 1:80 and 1:160. Anti-cardiolipin antibodies were within normal limits. Assays for anti-cyclic citrullinated peptide (CCP), anti-double-stranded DNA, and anti-extractable nuclear antigen (ENA) antibodies were negative. Additionally, cerebral spinal fluid (CSF) assays for varicella zoster virus, cytomegalovirus, and Epstein-Barr virus were negative.

At the tertiary care center additional imaging was performed. On repeat MRI, the previously noted cervical and intracranial left vertebral artery dissection was confirmed, as was the stenosis and dilatation of the right vertebral artery, the right carotid aneurysm/pseudoaneurysm, and the left subclavian abnormality. In addition, a possible dissection of the left internal carotid artery was noted due to signal abnormality along the posterolateral aspect of that vessel. Brain CTA showed fusiform dilatation of the proximal right A2 segment, irregular and attenuated M1 arteries bilaterally with focal dilatation at the right M1-M2 junction and bilateral narrowing of the proximal M2 arteries. The P1 segments were hypoplastic and bilateral stenoses were present in the P3 segments. None of these intracranial findings were appreciated from the initial MRA.

The patient was discharged one week after his initial admission. Upon discharge, he was still experiencing headaches if he did not take Fioricet. When he presented to his primary care physician three weeks after discharge, his headaches had resolved but he continued to feel fatigued on his regimen of anti-hypertensive medications. Renal artery imaging was planned to evaluate for renal artery stenosis as an etiology of this patient's hypertension. The patient returned to work and is planning to quit smoking. He also underwent genetic testing at the tertiary care center, revealing a diagnosis of Ehlers-Danlos syndrome, type IV.

DOI: 10.2484/rcr.2008.v3i2.172

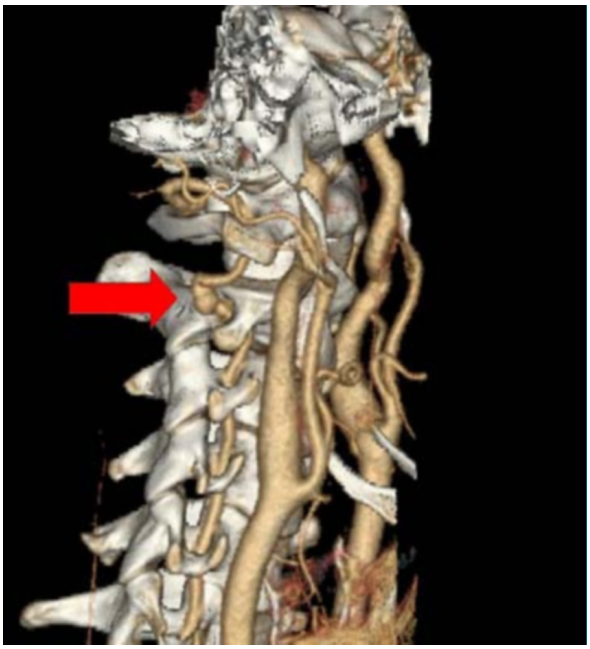

Figure 4. Three-dimensional reconstruction from neck CT, demonstrating saccular dilatation of the right vertebral artery.

Discussion

Ehlers-Danlos syndrome, type IV, or vascular Ehlers-Danlos syndrome, is an autosomal dominant disorder of connective tissue that mainly affects the arteries and digestive tract. The syndrome is caused by mutations of the COL341 gene, which codes for type III collagen [1]. Because type III collagen is found in the walls of arteries and digestive tract, these mutations predispose patients with vascular Ehlers-Danlos syndrome to arterial dissection and gastrointestinal perforations [2]. The prevalence of vascular Ehlers-Danlos syndrome is estimated from 1/500,000 to 1/100,000 [3, 4].

The clinical features of vascular Ehlers-Danlos syndrome include distinctive facies, skin findings, and bleeding abnormalities. Patients may exhibit a facial pattern referred to as acrogeria in which the faces appears to be prematurely aged, with decreased subcutaneous adiposity. This pattern presents with sunken cheeks, well-defined cheekbones, and prominence of the eyes. Additionally, these patients tend to have thin lips and noses. Patients with vascular Ehlers-Danlos syndrome are prone to ecchymoses and can have thin skin through which veins are easily visualized [1]. Further, bleeding time may be increased [4]. Although some patients

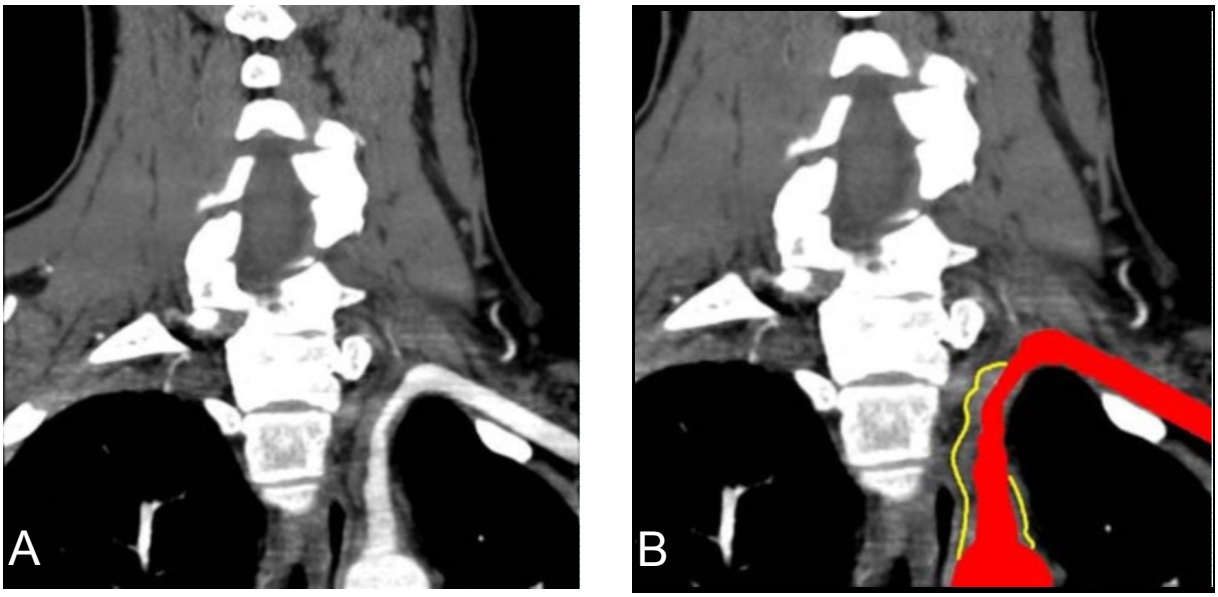

Figure 5A-B. Coronal CT with contrast, demonstrating narrowing of the left subclavian artery (without color in 5A, filled in red in 5B) with a surrounding crescent of soft tissue density (without color in 5A, outlined in yellow in 5B).

DOI: 10.2484/rcr.2008.v3i2.172

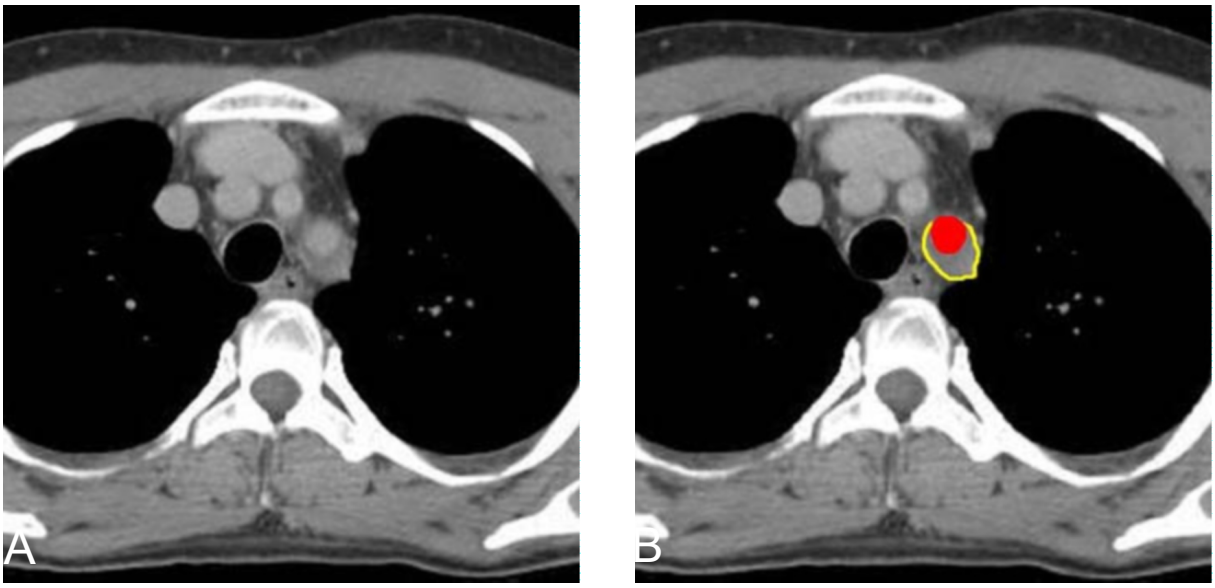

Figure 6A-B. Axial CT with contrast, demonstrating narrowing of the left subclavian artery (without color in 6A, filled in red in 6B) with a surrounding crescent of soft tissue density (without color in 6A, outlined in yellow in 6B).

exhibit hypermobility of the joints, this feature is less common and less severe than in other subtypes of Ehlers-Danlos syndrome [5]. The diagnosis is made by clinical presentation, biochemical studies of collagen, cDNA sequencing, and/or histology [4].

The major complications of vascular Ehlers-Danlos syndrome include rupture of the arteries and the bowel and other viscera. Due to the type III collagen defect, thin arterial walls are prone to dissection, pseudoaneurysms, and occasional fusiform aneurysms, most often involving the medium and large-sized vessels [4,6,7]. Most commonly affected are the carotid arteries, the vertebral arteries, the aorta and its primary branches, and the visceral arteries [4,6,8,9,10]. Vascular complications carry the highest chance of mortality. Weakness of the walls of the digestive track can lead to spontaneous rupture of the bowel, especially of the sigmoid colon [11]. Additional complications of vascular Ehlers-Danlos syndrome include rupture of the gravid uterus and lesions of the pleura and pulmonary parenchyma [5,10]. By age 40, 80% of patients will be affected by complications of vascular Ehlers-Danlos syndrome, resulting in a median age of death of 48 years old [11]. Thus, younger patients presenting with ischemic stroke, intracranial hemorrhage, or visceral perforation should be evaluated for further signs and symptoms of vascular Ehlers-Danlos syndrome [12].

Radiologic findings of Ehlers-Danlos syndrome generate a differential diagnosis of several other conditions including vasculitides, other connective tissue disorders and fibromuscular dysplasia (Table 1). However, there are characteristic anatomical and radiologic patterns of affected vessels that help narrow the differential diagnosis. A case review of patients clinically diagnosed with vascular Ehlers-Danlos found radiologic abnormalities including, in decreasing order of prevalence, aneurysms, dissections, ectasias, and occlusions [10].

There is continuing debate as to whether the vascular abnormalities found in patients with Ehlers-Danlos syndrome represent true or false aneurysms; dissection and vascular rupture with hematoma formation are both common complications [4,6]. Most of the morbidity and mortality in this illness likely originates from arterial dissections and ruptures, not from aneurysms, since dissections and ruptures are both unpredictable and difficult to repair [4]. The high likelihood of dissection and

DOI: 10.2484/rcr.2008.v3i2.172

Table 1. Differential diagnosis of vasculitides and connective tissue disorders

Primary vasculitis syndromes:
- Wegener's granulomatosis
- Chrug-Strauss syndrome
- Polyarteritis nodosa
- Microscopic polyangiitis
- Giant cell arteritis
- Takayasu's arteritis
- Henoch-Schonlein purpura
- Idiopathic cutaneous vasculitis
- Essential mixed cryoglobulinemia
- Behcet's syndrome
- Isolated vasculitis of the CNS
- Cogan's syndrome
- Kawasaki disease

Secondary vasculitis syndromes:
- Drug-induced vasculitis
- Serum sickness
- Vasculitis associated with other primary diseases
- Infection
- Malignancy
- Rheumatic disease

Heritable connective tissue disorders:
- *Marfan's syndrome*
- *Ehlers-Danlos syndrome*
- *Pseudoxanthoma elasticum*
- *osteogenesis imperfecta*
- *annuloaortic ectasia*
- *Familial aneurysms*

Nonheritable connective tissue disorders:
- *Systemic Lupus Erythmatosus*
- *Rheumatoid arthritis*
- *Ankylosing spondylitis*
- *Cardiovascular syphilis*
- *Systemic sclerosis (scleroderma)*
- *Primary systemic sclerosis of the heart*
- *Polymyositis and Dermatomyositis*
- *Polyarteritis nodosa*
- *Giant cell arteritis*
- *Churg-strauss vasculitis*
- *Antiphospholipid antibody syndrome*

rupture is supported by measurements of increased wall stress secondary to thin intima and media in patients with Ehlers-Danlos IV as compared with controls [13].

One of the challenges in identifying and clinically observing Ehlers-Danlos is that there are reports of vascular rupture during catheterization and arteriography, which in the past limited diagnostic studies [14,15]. However, as with this patient, non-invasive studies such as CTA, MRA, or Doppler sonography can yield valuable clinical data without invasive risks [16,17].

Treatment for vascular Ehlers-Danlos syndrome includes symptomatic management and prophylactic measures. Surgery to correct aneurysms or dissections can lead to significant procedure-related morbidity and mortality, both during these vascular operations and in the post-operative period, including exsanguinating hemorrhage, post-operative bleeding, aneurysms, disruption, and graft thrombosis [6]. Thus close observation is preferred in lieu of surgery whenever possible. When surgical intervention is necessary, direct repairs with closure not producing tension on the vessel are favored, and repeated non-invasive imaging should be performed post-operatively [17].

Clinical recommendations for patients with Ehlers-Danlos should include avoidance of intense physical activity and medications that interfere with platelet function or coagulation. Genetic counseling and screening of family members is advised [12]. Hypertension should be well-controlled to reduce the stress on already fragile vessels, and the patient's kidneys should be imaged to rule out renal artery stenosis secondary to vascular compromise, especially if such stenosis leads to hypertension.

DOI: 10.2484/rcr.2008.v3i2.172

References

1. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ: Ehlers-Danlos syndromes: revised nosology. Am J Med Genet. 1998 Apr;77:31-7. [PubMed]

2. Pope FM, Martin GR, Lichtenstein JR, Penttinen R, Gerson B, Rowe DW, McKusick VA: Patients with Ehlers-Danlos syndrome type IV lack type III collagen. Proc Natl Acad Sci. USA 1975 Apr;72:1314-6. [PubMed]

3. Barabas AP: Vascular complications in the Ehlers-Danlos syndrome, with special reference to the "arterial type" or Sack's syndrome. J Cardiovasc Surg (Torino). 1972 Mar-Apr;13:160-7. [PubMed]

4. Germain, DP. Ehlers-Danlos Type IV. Orphanet Journal of Rare Diseases. 2007 Jul 19;2:32. [PubMed]

5. Bravo JF, Wolff C: Clinical study of hereditary disorders of connective tissues in a Chilean population: joint hypermobility syndrome and vascular Ehlers-Danlos syndrome. Arthritis Rheum. 2006 Feb;54(2):515-23. [PubMed]

6. Oderich GS, Panneton JM, Bower TC, et al: The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30-year experience. J Vasc Surg. 2005 Jul;42(1):98-106. [PubMed]

7. Bergqvist D: Ehlers-Danlos type IV syndrome. A review from a vascular surgical point of view. Eur J Surg. 1996 Mar;162(3):163-70. [PubMed]

8. Schievink WI, Michels VV, Piepgras DG: Neurovascular manifestations of heritable connective tissue disorders: a review. Stroke 1994;25:889-903. [PubMed]

9. Schievink WI: Cerebrovascular Involvement in Ehlers-Danlos Syndrome. Curr Treat Options Cardiovasc Med. 2004 Jun;6(3):231-6. [PubMed]

10. Zilocchi M, Macedo TA, Oderich GS, Vrtiska TJ, Biondetti PR, Stanson AW: Vascular Ehlers-Danlos Syndrome: Imaging Findings. AJR Am J Roentgenol. 2007 Sep;189(3):712-9. [PubMed]

11. Pepin M, Schwarze U, Superti-Furga A, Byers PH: Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. N Engl J Med. 2000 Mar 9;342(10):673-80. [PubMed]

12. Germain DP, Herrera-Guzman Y: Vascular Ehlers-Danlos syndrome. Ann Genet. 2004 Jan-Mar;47(1):1-9. [PubMed]

13. Boutouyrie P, Germain DP, Fiessinger JN, Laloux B, Perdu J, Laurent S: Increased carotid wall stress in vascular Ehlers-Danlos syndrome. Circulation. 2004 Mar 30;109(12):1530-5. [PubMed]

14. Slingenberg EJ: Complications during intravascular diagnostic manipulations in the Ehlers-Danlos syndrome. Neth J Surg. 1980;32(2):56-8. [PubMed]

15. Mirza FH, Smith PL, Lim WN: Multiple aneurysms in a patient with Ehlers-Danlos syndrome: angiography without sequelae. AJR Am J Roentgenol. 1979 Jun;132(6):993-5. [PubMed]

16. Germain DP: Clinical and genetic features of vascular Ehlers-Danlos syndrome. Ann Vasc Surg. 2002 May;16(3):391-7. [PubMed]

17. Germain DP: The vascular Ehlers-Danlos syndrome. Curr Treat Options Cardiovasc Med. 2006 Apr;8(2):121-127. [PubMed]

DOI: 10.2484/rcr.2008.v3i2.172