OPEN

Cyanosis With Dysautonomia Mimics Raynaud Disease

Alyxandra Morgan Soloway, BS, BA, MS4, Nicholas L. DePace, MD, FACP, FACC,† Joseph Colombo, PhD,‡ and Stephen Soloway, MD, FACP, FACR, CCD§*

CLINICAL IMAGES MANUSCRIPT

Patients with Ehlers-Danlos syndrome often present with discoloration of distal extremities, suggesting Raynaud disease. They are known to have an increased incidence of dysautonomia.[1] A 16-year-old white female adolescent presented with purple feet and toes. The photos (Figs. 1, 2) show her purple feet and toes (cyanosis). Cyanosis, which may be due to deoxygenated blood from venous pooling, gives the appearance that may be confused with Raynaud disease. This prompted her rheumatology consultation for Raynaud disease. Her toes and feet felt cold to the touch; however, they were not worsened by the cold. The patient's history and physical revealed no evidence to suggest autoimmune disease. Specifically, there was no history of triple phase color response, dysphagia, dyspnea, or muscle weakness. Clinical examination revealed no sclerodactyly, telangiectasia, periungual erythema, digital infarction, nodules, or calcinosis, and analysis of nailfold capillaries was normal. Her pertinent laboratory results included negative anti–nuclear antibodies, anti–double-stranded DNA antibody, anti–extractable nuclear antigen, and Ro and La antibodies (SSA and SSB, respectively); negative rheumatoid factor and cyclic citrullinated peptide; negative anti–topoisomerase 1 antibodies (SCL70), anti–centromere antibodies, RNA polymerase III antibodies (RNA POL3), and anti–JO-1 antibody; normal serum protein electrophoresis; an erythrocyte sedimentation rate (ESR 2) of 2 mm/h; normal C-reactive protein (CRP 1, mg/L) level; a white blood cell count of 6.4 cpl; a hematocrit 39%; and a platelet count of 245,000/μL. Additional findings included hypermobile wrist and elbow, patella-femoral laxity, velvet skin texture and increased laxity, easy bruising, miosis using contact lens, and off-white sclera. With primary family history, the additional findings helped to confirm Ehlers-Danlos syndrome.

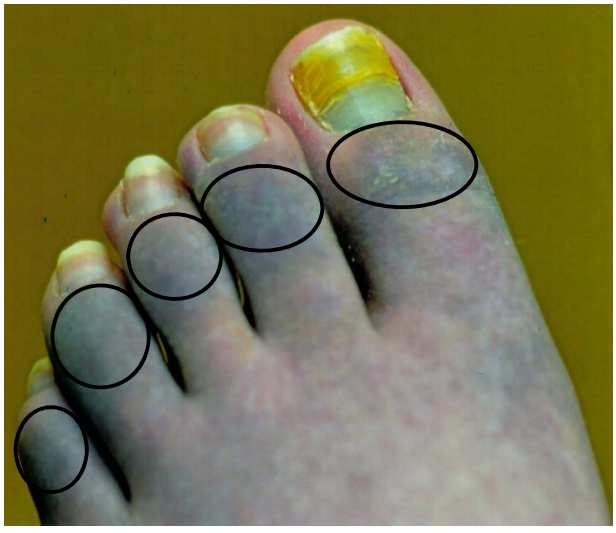

FIGURE 1.

Parasympathetic and sympathetic (P&S) nervous system testing[2] was performed. This 16-year-old patient demonstrated normal P&S activity and normal sympathovagal balance at rest (as most do). As the additional P&S monitoring with challenge revealed, the abnormalities (dysautonomia) were not demonstrated at rest. The postural change (stand) challenge revealed (alpha-) sympathetic nervous system insufficiency or withdrawal that is highly associated with venous pooling.[3] Excessive vagal, or parasympathetic, activity was documented during the Valsalva challenge (a series of short Valsalva maneuvers, less than 15 seconds, which normally stimulates only beta-sympathetic activity) indicating an additional cause for poor peripheral profusion.[2] This patient was treated with very low-dose nortriptyline (used as an anticholinergic) for the parasympathetic excess, and support hose, increased fluid intake, and low-dose midodrine (an alpha-adrenergic agonist and vasopressor) for the sympathetic withdrawal and venous pooling. The patient's circulation has improved as evidenced by warmer toes and feet and reduced distal extremity cyanosis.

This case is an example of the importance of differentiating Raynaud disease mimics and awareness of dysautonomia. The mechanism for P&S nervous system dysfunction is typically from small fiber neuropathy.[4] Vasovagal syncope[5] with postural orthostatic tachycardia syndrome[2] is a combination of 3 stand abnormalities, is frequently documented in Ehlers-Danlos syndrome patients, and is a common cause for their risk of Raynaud disease–like

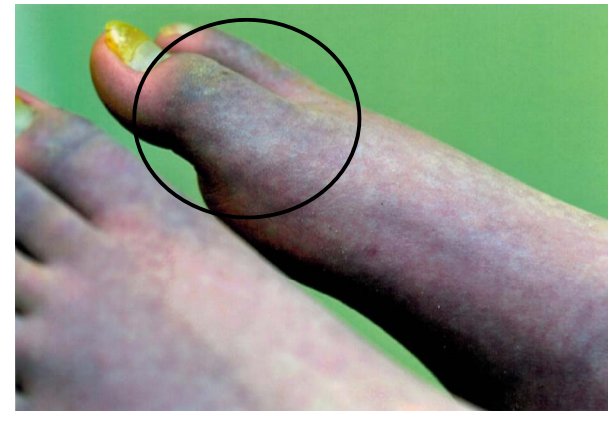

FIGURE 2.

From the *American University of the Caribbean, Coral Gables, FL; †Pennsylvania Hospital of the University of Pennsylvania Health System, Pennsylvania, PA; ‡Parasympathetic and Sympathetic Nervous System Consultant, Franklin Cardiovascular Associates, Pa, Sewell; and §Stephen Soloway, Rheumatology, Vineland, NJ.

The authors declare no conflict of interest.

Correspondence: Stephen Soloway, MD, FACP, FACR, CCD, 2848 S Delsea Dr, Suite 2C, Vineland, NJ 08360. E-mail: ssoloway@drsoloway.com.

ISSN: 1076-1608
DOI: 10.1097/RHU.0000000000001107

symptoms. Often for patients with dysautonomia and Raynaud disease–like symptoms, the Raynaud disease–like symptoms are due to venous pooling, which is another indication of autonomic dysfunction.

REFERENCES

1. De Wandele I, Rombaut L, Leybaert L, et al. Dysautonomia and its underlying mechanisms in the hypermobility type of Ehlers-Danlos syndrome. *Semin Arthritis Rheum*. 2014;44:93–100.
2. Colombo J, Arora RR, DePace NL, et al. Clinical autonomic dysfunction: measurement, indications, therapies, and outcomes. *Springer Science + Business Media, New York, NY*. 2014.d;125–135.
3. Arora RR, Bulgarelli RJ, Ghosh-Dastidar S, et al. Autonomic mechanisms and therapeutic implications of postural diabetic cardiovascular abnormalities. *J Diabetes Sci Technol*. 2008;2: 645–657.
4. Cazzato D, Castori M, Lombardi R, et al. Small fiber neuropathy is a common feature of Ehlers-Danlos syndrome. *Neurology*. 2016;87: 155–159.
5. DePace NL, Bateman JA, Yayac M, et al. Improved patient outcomes by normalizing sympathovagal balance: differentiating syncope-precise subtype differentiation leads to improved outcomes. *Cardiol Res Pract*. 2018,2018:9532141.