Received: 10 June 2019 | Revised: 20 June 2019 | Accepted: 8 July 2019

DOI: 10.1111/chd.12824

ORIGINAL ARTICLE

Congenital Heart Disease WILEY

Utilization of echocardiography in Ehlers-Danlos syndrome

Kristina K. Rauser-Foltz[1] | Lois J. Starr[2] | Anji T. Yetman[1]

[1]Division of Cardiology, Department of Pediatrics, Children's Hospital and Medical Center, Omaha, Nebraska

[2]Division of Clinical Genetics, University of Nebraska Medical Center, Children's Hospital and Medical Center, Omaha, Nebraska

Correspondence
Anji T. Yetman, MD, Division of Cardiology, Department of Pediatrics, Children's Hospital and Medical Center, 8200 Dodge St, Omaha NE 68114.
Email: ayetman@childrensomaha.org

Abstract

Objectives: This study assessed the frequency and utility of echocardiographic examination in patients with all forms of Ehlers-Danlos syndrome and sought to identify clinical variables associated with an abnormal echocardiogram.

Design/setting: This was a retrospective study of all patients carrying a diagnosis of Ehlers-Danlos syndrome of any type who were evaluated by a pediatrician or pediatric subspecialist at a single tertiary medical center with an affiliated children's hospital during the period January 2013 to December 2018.

Patients: Chart review was performed on all patients carrying a diagnosis of Ehlers-Danlos syndrome in the electronic medical record.

Outcome Measures: Data from genetics examination, cardiovascular examination where applicable, genetic test results when available, and echocardiography were recorded.

Results: Of 262 patients identified, echocardiography and cardiac evaluation were common occurring in 90% and 50% of patients with any form of Ehlers-Danlos syndrome. Cardiovascular complications occurred in 50% of patients with vascular Ehlers-Danlos syndrome but echocardiography was normal in all. Aortic dilation was common in classic Ehlers-Danlos syndrome but absent in hypermobile Ehlers-Danlos syndrome. Mitral valve prolapse and bicuspid aortic valve occurred at the same incidence as the general population. Cardiac symptoms were present in 12% but did not correlate with abnormal cardiac structure. Presentation with symptoms of musculoskeletal pain was inversely related to the presence of cardiac pathology.

Conclusions: In light of the absence of cardiac pathology in patients with hypermobile Ehlers-Danlos syndrome, routine cardiac evaluation and echocardiography are not required for patients with hypermobile Ehlers-Danlos syndrome.

KEYWORDS

aneurysm, aorta, echocardiography, Ehlers-Danlos syndrome

1 | INTRODUCTION

Ehlers-Danlos (EDS) is a group of heritable connective tissue disorders.[1] Despite some overlapping minor clinical features, namely joint hypermobility, skin hyperextensibility, and tissue fragility, major cardiovascular features are limited to only one or two of six major subtypes.[1,2] While this may be well known to those routinely providing care to these patients, a single eponym for multiple distinct disorders requiring different management strategies provides a great deal of confusion for patients and providers alike.

Hypermobile Ehlers-Danlos syndrome (hEDS) is a commonly diagnosed disorder devoid of significant cardiac complications.[3] While the overall prevalence of all types of EDS is estimated at 1 in 5000 persons worldwide, more than 90% of these patients will have hEDS.[4] The diagnosis of hEDS is clinical as there is no confirmatory laboratory test. In contrast to hEDS, the vascular form of

Ehlers-Danlos syndrome (vEDS) is quite rare with a prevalence of 1/50 000 and is associated with significant morbidity and mortality.[2] While the diagnosis of vEDS can be suspected on the basis of clinical features, it is confirmed with genetic testing showing a *COL3A1* mutation.[4] Patients with vEDS have characteristic facial features, and generalized hypermobility is not a mainstay of the diagnosis.[2]

The role of cardiac evaluation and echocardiography in assessing patients with hEDS has been historically unclear[1] but contemporary data notes no associated structural cardiac pathology of significance in these patients.[5] We sought to determine whether this data were reflected in current practice patterns by assessing the frequency of cardiac referral and echocardiography in patients with EDS. In addition we sought to ascertain whether echocardiography was of any additional value to standard history and examination in these patients.

2 | METHODS

An IRB approved retrospective chart review was performed. Clinical and echocardiographic databases were reviewed and all patients with a confirmed or suspected diagnosis of Ehlers-Danlos syndrome of any type seen during the period January 2013 to December 2018 were identified. Variables extracted from the clinical records included age, gender, primary symptom, Beighton score, type of Ehlers-Danlos suspected, family history of aneurysm, genetic testing results where applicable, subspecialty type of provider referring to cardiology, cardiovascular exam findings, and final clinical diagnosis if different than suspected diagnosis prior to cardiac evaluation.

Echocardiograms were reviewed and the following recorded: age(s) at echocardiogram, specialty of provider ordering the study, number of studies per patient, presence or absence of aortic dilation defined as a *z* score > 2[6] presence or absence of valvar pathology and presence or absence of other significant findings defined as echocardiographic findings requiring a follow-up study. Aortic dimensions were taken in the parasternal long axis view in systole and obtained inner edge to inner edge.[7] In those patients with Ehlers-Danlos who had repeat echocardiography, progression, or normalization of aortic dilation was tracked over time.

Patients were grouped into those with classic, hypermobile, vascular, or other types of EDS based on clinical documentation at the time the initial referral was made for cardiology evaluation and/or echocardiography. Patients were excluded if there was insufficient documentation to ascertain the type of EDS suspected or if they had an unrelated congenital cardiac defect that required ongoing cardiac care and imaging. Data from these patients were excluded so as to not inflate the prevalence and utilization data. Final diagnosis after cardiac evaluation ± echocardiography, was noted and differences from preliminary diagnosis explored.

Descriptive statistics were represented as means with standard deviations and medians with ranges as appropriate. The following factors were explored as possible clinical correlates of an abnormal echocardiogram: presence of a family history of aneurysm, abnormal cardiac examination, Beighton score, age, gender, presenting symptom, and EDS type at cardiac referral. T test, Chi square analyses and Fisher's exact test were used to assess differences between clinical variables for those with a normal vs abnormal echocardiogram as appropriate.

3 | RESULTS

A total of 262 patients from 223 families were diagnosed with some type of EDS during the 6 year study period at a mean age of 12.1 ± 9.0 years. There were 97 males and 165 females. Of those, four patients were excluded for unrelated cardiac pathology requiring periodic echocardiography including four with chemotherapy-induced cardiomyopathy, one with myocarditis, one with a large secundum atrial septal defect, and one with atrioventricular septal defect. Clinical ± echocardiographic data were reviewed on the remaining 258 patients of whom 236 (91%) were suspected of having hEDS, 16 classic EDS, 4 vEDS and 2, another form of EDS (1 kyphoscoliotic and 1 dermatospraxis).

Of 258 patients, cardiac evaluation was performed in all patients with classic and vascular EDS as well as 120 of 236 (51%) patients suspected of having hypermobile EDS. A family history of aortic aneurysm ± dissection was present in 19 families. Abnormal cardiovascular examination was present in 8 of 120 (6%) patients. The primary presenting complaint included asymptomatic hypermobility in 80, diffuse pain in 44, skin abnormalities in 31, joint dislocations in 17, positive family history of EDS in 12, dizziness/presyncope in 11, palpitations in 6, dysmorphia in 3, ocular abnormalities in 3, hypotonia in 2, vascular complication in 2, other in 13 and unknown in 34. No subjects were diagnosed with reflex sympathetic dystrophy/complex regional pain syndrome. The primary complaint in 30 patients (12%) was cardiac in origin.

Genetic testing was performed in 74 of 262 patients (28%) suspected of having any form of EDS. Results in those with a presumed diagnosis of EDS other than hEDS included the following pathogenic variants: *COL3A1* mutation in four, a homozygous *PLOD1* mutation in one, *CHST14* mutation in one, and *COL5A1* mutation in seven. In those suspected of having hEDS, the following pathogenic variants or variants of uncertain significance were found: *OPA1* in one, *FBN5* in one, *MYLK* in two families, *COL9A1* in one, *COL 11A1* in four families, *COL1A1* in one, *TNXB* in two families and MT-RNR in one.

A total of 315 echocardiograms were performed over the 6 year study period with an average of 1 (1-6) study per patient. All but 28 of 236 (11%) with hEDS underwent echocardiography as did all patients with other forms of EDS. The frequency of echocardiographic assessment was significantly different between those with vEDS vs classic EDS vs hEDS (4 [1-6] vs 2 [1-6] vs 1 [0-5], $F = 26.1$, $P < .0001$). Despite a normal first echocardiogram, 44 (18%) patients with hEDS underwent at least one additional echocardiogram during the study period.

Echocardiographic abnormalities were identified in 17 (6%) patients undergoing echo for an initial suspicion of any form of EDS.

Abnormalities included aortic dilation in 12 (4%), mitral valve prolapse with mild mitral insufficiency in 3, patent ductus arteriosus in 1, and bicuspid aortic valve in 3 patients (2 of whom had associated aortic dilation). Echocardiographic findings per confirmed type of EDS are shown in Table 1.

Of four patients with vEDS, all had normal serial echocardiograms. The single patients with the kyphoscoliotic and musculocontractural forms of EDS both had aortic dilation. Mild to moderate aortic dilation was also seen in 7 of 16 patients (43%) with classic EDS. Four patients initially suspected to have hEDS, but subsequently genetically confirmed to have a different disorder (mitochondrial myopathy in two, MYLK familial thoracic aortic aneurysm syndrome in one, and cutis laxa in one) had mild aortic dilation. After excluding patients with positive genetic testing for other disorders, there were no patients with hEDS with aortic dilation. Cardiovascular complications occurred in six patients in our cohort—two with vEDS and four with classic EDS (cEDS). One patient with vEDS developed a spontaneous coronary artery branch rupture and carotid artery dissection and the other developed a spontaneous iliac artery and radial artery dissection. Two patients with cEDS and bicuspid aortic valve developed significant aortic dilation requiring surgical intervention with ascending aortic replacement, and two patients with cEDS required surgical intervention for peripheral arterial aneurysm ruptures—one in the popliteal artery and the other in the superior mesenteric artery. No patient with hEDS developed a cardiovascular complication.

In the hEDS cohort, which represented the vast majority of the patients, echocardiograms were primarily ordered by pediatricians (45%), cardiologists (33%), geneticists (10%), rheumatologists (5%), and other providers (7%).

In addition to cEDS, the only other predictors of an abnormal echocardiogram in the entire cohort included family history of aneurysm (47% vs 4%, $P < .001$), and abnormal cardiac examination (85% vs 5%, $P < .001$). Patients whose primary symptom was pain were less likely to have an abnormal echo than those without pain (0% vs 20%, $P = .008$).

4 | DISCUSSION

hEDS is a common disorder not associated with aortic dissection.[3] We found substantial utilization of echocardiography in patients with suspected hEDS with our center performing close to 300 normal echocardiograms in patients over the 6 year period. As previously demonstrated we found that patients with hEDS did not have significant, or any, aortic disease once other genetic conditions were ruled out. The impetus for testing in these patients comes from patients and physicians alike. The name EDS invokes concern given the eponym's association with lethal vascular pathology. To further confuse matters the 2017 hEDS diagnostic guidelines[1] now include aortic root dilation as a supportive feature for a diagnosis of hEDS despite the lack of evidence for significant aortic pathology in these patients. At present, there are no published reports of thoracic aortic aneurysms requiring surgical intervention or aortic dissection occurring in patients with hEDS.

TABLE 1 Echocardiographic Findings by final diagnosis of Ehlers-Danlos syndrome type

Diagnosis	hEDS	cEDS	vEDS	Other EDS
Mitral valve prolapse	2/208	1/16	0/4	0/2
Bicuspid Aortic Valve	0/208	3/16	0/4	0/2
Aortic Dilation	0/208	7/16	0/4	2/2

Abbreviations: cEDS, classic Ehlers-Danlos syndrome; hEDS, hypermobile Ehlers-Danlos syndrome; vEDS, vascular Ehlers-Danlos syndrome. Other EDS included type kyphoscoliotic and dermatospraxis.

We found that over 10% of patients with hEDS present with cardiac symptoms and thus are likely to have some interaction with a pediatric or internal medicine cardiologist. As such, it is important that cardiologists are well versed in the various types of Ehlers-Danlos syndrome in order to allow for appropriate testing.

Perhaps somewhat surprising, none of the patients with vEDS had an abnormal echocardiogram during the course of follow-up. This is consistent with the literature. Despite the high risk of vascular dissection the majority of patients with vEDS will not have aortic root dilation on imaging studies.[8] Aortic aneurysms may occur anywhere throughout the vascular tree and dissection may occur in the absence of aneurysm formation. Because echocardiography only visualizes a small portion of the arterial tree, it is not an adequate tool for surveillance of these patients and may provide false reassurance.

The incidence of bicuspid aortic valve found in this study (1%) as well as that of mitral valve prolapse are in keeping with previously reported statistics for the general population.[9-12]

We found a relatively high incidence of mild to moderate aortic dilation in patients with cEDS. Aortic root dilation aneurysms and branch vessel aneurysms have been previously reported in this disorder[13-15] albeit less commonly than in vEDS. We also found branch vessel aneurysms in these patients as young as adolescence—one with a superior mesenteric artery aneurysm with dissection and one with a popliteal artery dissection. Both patients presented with symptoms and successful surgical intervention was performed. Surveillance methods for these patients have not been established.

In light of our findings and those of other large studies assessing the results of echocardiographic evaluation in patients with EDS, it appears that echocardiography may play a role in the following patients with hEDS: patients with a positive family history for aneurysms or abnormal auscultatory examination, particularly in those who do not have pain as their primary symptom. For the vast majority of patients with hEDS, echocardiography adds little value above and beyond a careful history and examination. Educational efforts should be made to highlight the differences between hEDS and the other forms of EDS which can be associated with cardiac pathology. If significant aortic dilation is seen in a patient with a diagnosis of hEDS, other causes of aortic dilation should be thoroughly investigated. In contrast, echocardiography remains an important diagnostic tool for patients with cEDS and vEDS. Unfortunately, without a distinct name change, uncertainty is likely to persist and result in continued misuse of clinical resources.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Was responsible for data collection, data analysis, and manuscript writing: Kristina Rauser-Foltz
Was responsible for data analysis and manuscript review and revision: Lois Starr
Was responsible for study conception, study design, data analysis, and manuscript writing: Anji Yetman

ORCID

Anji T. Yetman https://orcid.org/0000-0001-6853-578X

REFERENCES

1. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175(1):8-26.
2. Byers PH, Belmont J, Black J, et al. Diagnosis, natural history, and management in vascular Ehlers-Danlos syndrome. *Am J Med Genet C Semin Med Genet*. 2017;175(1):40-47.
3. Asher SB, Chen R, Kallish S. Mitral valve prolapse and aortic root dilation in adults with hypermobile Ehlers-Danlos syndrome and related disorders. *Am J Med Genet A*. 2018;176(9):1838-1844.
4. Byers P.Vascular Ehlers-Danlos syndrome. https://www.ncbi.nlm.nih.gov/books/NBK1494/. Updated 2019. Accessed April 20, 2019.
5. Ritter A, Atzinger C, Hays B, et al. Natural history of aortic root dilation through young adulthood in a hypermobile Ehlers-Danlos syndrome cohort. *Am J Med Genet A*. 2017;173(6):1467-1472.
6. Colan S. *Z Score Calculator*. Boston Children's Hospital Heart Center. http://zscore.chboston.org/. Accessed May 9, 2019.
7. Lopez L, Colan SD, Frommelt PC, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the pediatric measurements writing group of the American society of echocardiography pediatric and congenital heart disease council. *J Am Soc Echocardiogr*. 2010;23(5):465-495; quiz 576-7.
8. Chu LC, Johnson PT, Dietz HC, et al. Vascular complications of Ehlers-Danlos syndrome: CT findings. *AJR Am J Roentgenol*. 2012;198(2):482-487.
9. Flack JM, Kvasnicka JH, Gardin JM, Gidding SS, Manolio TA, Jacobs DR Jr. Anthropometric and physiologic correlates of mitral valve prolapse in a biethnic cohort of young adults: the CARDIA study. *Am Heart J*. 1999;138(3 Pt 1):486-492.
10. Hepner AD, Ahmadi-Kashani M, Movahed MR. The prevalence of mitral valve prolapse in patients undergoing echocardiography for clinical reason. *Int J Cardiol*. 2007;123(1):55-57.
11. Freed LA, Levy D, Levine RA, et al. Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med*. 1999;341(1):1-7.
12. Basso C, Boschello M, Perrone C, et al. An echocardiographic survey of primary school children for bicuspid aortic valve. *Am J Cardiol*. 2004;93(5):661-663.
13. McDonnell NB, Gorman BL, Mandel KW, et al. Echocardiographic findings in classical and hypermobile Ehlers-Danlos syndromes. *Am J Med Genet A*. 2006;140(2):129-136.
14. Atzinger CL, Meyer RA, Khoury PR, Gao Z, Tinkle BT. Cross-sectional and longitudinal assessment of aortic root dilation and valvular anomalies in hypermobile and classic Ehlers-Danlos syndrome. *J Pediatr*. 2011;158(5):826-830.e1.
15. Wenstrup RJ, Meyer RA, Lyle JS, et al. Prevalence of aortic root dilation in the Ehlers-Danlos syndrome. *Genet Med*. 2002;4(3):112-117.

How to cite this article: Rauser-Foltz KK, Starr LJ, Yetman AT. Utilization of echocardiography in Ehlers-Danlos syndrome. *Congenital Heart Disease*. 2019;14:864–867. https://doi.org/10.1111/chd.12824