Ehlers-Danlos syndrome and postural tachycardia syndrome: a relationship study

Daniel Wallman, BSE, Janice Weinberg, D.Sc. and Anna Hohler, M.D.

Boston University School of Medicine, 72 East Concord Street, #A302, Boston, MA.

Introduction

- Postural Tachycardia Syndrome (POTS) is a condition caused by an underlying autonomic dysfunction.
- In a significant subset of POTS patients, no etiology can be identified, yet studies have linked joint hypermobility syndrome with POTS, providing a potential link between Ehlers-Danlos Syndrome (EDS) and POTS.
- EDS is a heterogeneous group of inherited abnormalities of connective tissue characterized by skin hyper-extensibility, joint hypermobility, and connective tissue fragility.
- This study focuses on establishing a relationship between EDS and POTS.

Materials and methods

- Medical records of 109 patients suffering from autonomic dysfunction exhibiting at least one POTS symptom were sorted based on those that had a POTS diagnosis and/or an EDS diagnosis.
- We established three subsets and compared the prevalence of EDS within each:
  1. Patients diagnosed with POTS
  2. Patients who did not have POTS but who do have autonomic dysfunction
  3. The general population.
- EDS diagnoses of POTS patients were then confirmed by a geneticist followed by genetic screening.

Results

General Population Comparison	Group	N	N Pts with EDS	Prevalence	95% CI Lo	95% CI Hi	P Value*
	With POTS	36	7	18%	8%	34%	<0.0001
	Without POTS	70	3	4%	1%	12%	<0.0001
Group Comparison	**Test**			**OR**	**95% CI Lo**	**95% CI Hi**	**P Value**
	Odds Ratio			4.9	1.2	20.1	0.0329

Table 1: Prevalence of EDS amongst patients with and without POTS. * generated by comparing to the estimated prevalence of EDS in the general population (0.02%)

Above:

•The medical review revealed 39 (36 F: 3 M) patients with POTS (mean ± SD age, 32.5 ± 11.8 years) with 7 cases of EDS yielding a prevalence of 18% (95% exact CI: 8%, 34%), a highly statistically significant difference to the suggested prevalence of EDS in the general population at 1 in 5000, or 0.02% (p<0.0001) [Steinmen et al].

•70 patients (53 F: 17 M) without POTS (mean ± SD age, 51.1 ± 14.7 years) contained 3 cases of EDS, yielding a prevalence of 4% (95% exact CI: 1%, 12%), also a statistically significant difference to the general population (p<0.0001).

•The prevalence of EDS is significantly higher in the POTS group compared to the non-POTS group (p=0.0329) with an odds ratio comparing the odds of EDS for POTS versus non-POTS patients of 4.9 (95%CI: 1.2, 20.1).

Below:

•Patients diagnosed clinically with EDS were examined by a geneticist to confirm the diagnosis and determine the genetic etiology of EDS.

Patient	Genetic Consult Diagnosis	Genetic Testing
5	Positive, type unknown*	None
8	Positive, type unknown*	None
24	Positive for Classic subtype	Negative
26	Positive for Classic subtype	VUS: c.2331+16 G>A. on COL5A1.
30	Positive for Classic subtype or Vascular; may have Hypermobility	None
32	Positive for Classic subtype	Negetive
39	Positive for Classic subtype	VUS: c.787-15 G>A on COL5A1

Table 2: List of genetic consult and testing results.VUS = Variant of uncertain significance G = Guanine, A = Adenine. *consult performed at an external institution, confirmed with patient, but type details not provided.

Conclusions

- The prevalence of EDS amongst patients with POTS is 18%, a statistically significant result when compared to the suggested prevalence of 1 in 5000 in the general population [Steinmen et al].
- The prevalence of EDS amongst patients without POTS but with autonomic dysfunction is 4%, also a statistically significant result when compared to the suggested prevalence of EDS in the general population.
- Great vessels contain nerve bundles that reside in the tunica adventitia. A disruption of this layer via compromised connective tissue may disrupt the innervation, potentially causing the autonomic dysfunction witnessed in our patients.
- We suspect EDS may be a predictor of POTS and that there may be an additional underlying mechanism of POTS caused by the change in connective tissue from EDS.
- Future genetic research of these variants in a POTS and EDS positive population may yield interesting results and may shed more light on the underlying POTS mechanism.

Literature cited

1. E. Benarroch, "Postural Tachycardia Syndrome: A Heterogeneous and Multifactorial Disorder," *Mayo Clin. Proc.*, vol. 87, no. 12, pp. 1214–1225, Dec. 2012.
2. A. K. Thould and P. Beighton, "The Ehlers-Danlos Syndrome.," *Ann. Rheum. Dis.*, vol. 29, no. 3, pp. 332–333, 1970.
3. B. Steinmann, P. M. Royce, and A. Superti-Furga, "The Ehlers-Danlos syndrome," in in *Connective tissue and its heritable disorders: molecular, genetic and medical aspects*, 2nd ed., P. Royce and B. Steinmann, Eds. New York: Wiley-Liss, 2002, pp. 431–524.
4. P. C. Rowe, D. F. Barron, H. Calkins, I. H. Maumenee, P. Y. Tong, and M. T. Geraghty, "Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome.," *J. Pediatr.*, vol. 135, no. 4, pp. 494–9, 1999.
5. A. De Paepe and F. Malfait, "The Ehlers-Danlos syndrome, a disorder with many faces.," Clin. Genet., vol. 82, no. 1, pp. 1–11, Jul. 2012.
6. R. Wenstrup and A. De Paepe, "Ehlers-Danlos Syndrome , Classic Type," *GeneReviews*, 2007.
7. B. T. Tinkle, H. a Bird, R. Grahame, M. Lavallee, H. P. Levy, and D. Sillence, "The lack of clinical distinction between the hypermobility type of Ehlers-Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome).," *Am. J. Med. Genet. A*, vol. 149A, no. 11, pp. 2368–70, Nov.

Further information

Contact Daniel Wallman at dwallman@bu.edu or Dr. Anna Depold Hohler at Anna.Hohler@bmc.edu for further information.

Acknowledgments

BUSM Summer Research Program and the Neurology Department at BMC.