Ehlers-Danlos Syndrome in the University Hospital of Liège

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Introduction

Ehlers-Danlos Syndrome (EDS) is a common reason for consulting in clinical genetics. In our genetic consultations, we are confronted with an excessive numbers of patients referred for joint hypermobility and/or an electronic microscopy analysis of skin biopsies. In many cases, a dermatologist or a physiotherapist has already established a clinical diagnosis of hypermobility type EDS. As recently published by Malfait *et al.* [1], EDS hypermobility type diagnosis is based on clinical findings. Only in this context, a genetics consultation does not seem to be of additional value since no additional analyses are indicated to confirm the diagnosis.
The aim of this study was to characterize patients referred to clinical genetics consultations for EDS suspicion and evaluate the utility of genetics analysis.

Methods

We performed a retrospective observational study of the patients from the University Hospital of Liège who had come to a genetic consultation for Ehlers-Danlos syndrome or other collagenopathies between March 2016 (date of creation of the consultation dedicated to EDS) and December 2017. We performed a descriptive statistical analysis of demographic and clinical characteristics including reason for referral, referee, age, gender, Beighton score, Ehlers-Danlos syndrome associated clinical signs, family history, as well as the prescribed complementary tests (heart ultrasound, aortic angio MRI/scan, genetic testing).

Results

From March 2016 to December 2017, we have seen 143 patients in the collagenopathies consultation : 123 women and 20 men, with a mean age of 35.9 (± 14.1) years old.
111 patients (78.2%) were referred for an Ehlers-Danlos syndrome suspicion based on joint hypermobility. The other 32 patients were referred for collagenopathy suspicion (personal or family history of aneurysms), 5 of whom presented a marfanoid habitus.

Only two thirds of the patients presented joint hypermobility as assessed by the Beighton score : 60.8% (n=87) had a positive Beighton score higher than 5 (mean of 4.95 ± 2.90). This was associated with joint instability in most of the cases and generalized arthromyalgia. Only 19% (n=27) of the patients presented skin hyperextensibility, 28% (n=40) skin fragility with enlarged scars and only one case presented atrophic papyraceous scars. Among the other clinical signs, 11% (n=16) presented arachnodactyly and 14% (n=20) a high palate (Table 1).

Table 1 : Clinical characteristics of the patients seen in the collagenopathies consultation

Clinical characteristics	Number of patients
Dolichostenomelia	5.63% (n=8)
Repeated strain or luxation	64.08% (n=91)
Skin hyperelasticity	19.01% (n=27)
Scars	Atrophic scars : 0.7% (n=1) Marked scars : 27.97% (n=40) Stretch marks : 9.15% (n=13)
Pectus	Excavatum : 9.15% (n=13) Carinatum : 4.22% (n=6)
Varicose veins	11.27% (n=16)
Arachnodactyly	11.27% (n=16)
Abnormal palate	High : 14.08% (n=20) Hypertrophic : 0.7% (n=1)
Uvula	Elongated : 6.34% (n=9) Bifid : 1.41% (n=2)

Regarding family history, 81 patients (57.0%) had at least one relative with joint hypermobility. In 20 patients (14.1%) the family history was positive for vascular problems, five patients (3.5%) had a family history positive for auto-immune disorders and one patient (0.7%) had a relative with polycystic kidneys.

Table 2 : Cardiac ultrasound

Cardiac ultrasound results	n
Normal result	37
Ectasia of the ascending aorta	1
Mitral insufficiency	1
Dilatation of the ascending aorta	1
In progress	8
Total	**46**

A cardiac ultrasound (Table 2) was performed in 46 patients (28.9%) and other complementary tests (aortic angio MRI/scan, RX, …) were performed in 22 patients (15.5%).

Based on the presence of findings suggestive of an underlying genetic etiology, a genetic analysis was performed in 41 patients. Six (4.2%) tested positive (Table 3 and 4). The two patients presenting a *TGFB3* mutation were a mother and daughter with a Loeys-Dietz syndrome. The other three anomalies were variants of unknown significance. The duplication/deletion was not related to the symptoms of the patient.

Table 3 : Genetic tests

Genes tested	n
TAAD panel [2]	19
COL5A1 – COL5A2	11
COL1A1 – COL1A2	1
COL1A3	1
FBN1	1
TGFB3	1
RPS6KA3	1
CGH array	4
Total	**41**

[2] *The TAAD (thoracic aortic aneurysm and dissection) genes panel : ACTA2, BGN, COL3A1, FBLN4, ELN, EMILIN1, FBN1, FBN2, FLNA, FOXE3, LMOD1, LOX, MAT2A, MFAP5,MYH11,MYLK,NOTCH1, PLOD1, PRKG1,SKI, SCL2A10, SAMD2, SMAD3, SAMD4, TFGFB2, TGFB3,TGFBR1,TGBR2.*

Table 4 : Genetic results

Mutations founded	n
Normal result	30
c.899G (p.Arg300Gln) - *TGFB3*	2
c.1234C>T, p.(Arg412*) - *MYH11*	1
c.515C>T (p.Thr172Ile) - *SLC2A10*	1
c.1531T>C (p.Tyr511His) - *FBN1* + c.454C>T (p.Arg152Trp) - *TGFB3*	1
Duplication 22q11.21 + deletion Xp22.31	1
In progress	5
Total	**41**

We have diagnosed one patient with classical EDS with so far no molecular confirmation and we have diagnosed a familial Loeys-Dietz syndrome (mother and daughter). In three patients (2.2%), the genetic results were not conclusive (variants of unknown significance). Except for these rare cases where the consultation confirmed the presence of pathology, the majority of the evaluations only confirmed the already established diagnosis of benign hypermobility syndrome (57.0%) or excluded the presence of a collagenopathy (40.8%).

Conclusion

The vast majority (97.8%) of the patients referred for an EDS suspicion presented a hypermobility type or another non-genetic disorder, and a genetic consultation did not have any additional value. Since the diagnosis of hypermobile type of EDS is based on clinical findings, it is essential to make physiotherapists, rheumatologists and general practitioners aware of this. Specialized training regarding signs or symptoms suggestive of rare EDS type or other collagenopathies that can be diagnosed genetically, is essential. Referral criteria should be defined in order to select cases needing a clinical genetic evaluation.

[1] Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, Bloom L, Bowen JM, Brady AF, Burrows NP, Castori M, Cohen H, Colombi M, Demirdas S, De Backer J, De Paepe A, Fournel-Gigleux S, Frank M, Ghali N, Giunta C, Grahame R, Hakim A, Jeunemaitre X, Johnson D, Juul-Kristensen B, Kapferer-Seebacher I, Kazkaz H, Kosho T, Lavallee ME, Levy H, Mendoza-Londono R, Pepin M, Pope FM, Reinstein E, Robert L, Rohrbach M, Sanders L, Sobey GJ, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Wheeldon N, Zschocke J, Tinkle B. 2017, « The 2017 international classification of the Ehlers–Danlos syndromes », *Am J Med Genet Part C Semin Med Genet* ,175C, pp. 8–26.