Research in Developmental Disabilities 34 (2013) 873–881

Contents lists available at SciVerse ScienceDirect

Research in Developmental Disabilities

Clinical heterogeneity in patients with the hypermobility type of Ehlers-Danlos Syndrome

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ARTICLE INFO

Article history:
Received 28 July 2012
Received in revised form 6 November 2012
Accepted 21 November 2012
Available online 2 January 2013

Keywords:
Ehlers-Danlos syndrome
Hypermobility
Clinical heterogeneity
Non-musculoskeletal symptoms
Functional impairment
Pain experience

ABSTRACT

EDS-HT is a connective tissue disorder characterized by large inter-individual differences in the clinical presentation, complicating diagnosis and treatment. We aim to describe the clinical heterogeneity and to investigate whether differences in the symptom profile are also reflected as disparity in functional impairment and pain experience. In this study, 78 patients were asked to describe their symptoms due to EDS-HT. Next, a hierarchical cluster analysis was performed using the Jaccard measure of similarity to assess whether subgroups could be distinguished based on the symptoms reported. This analysis yielded 3 clusters of participants with distinct complaint profiles. The key differences were found in the domain of non-musculoskeletal complaints, which was significantly larger in cluster 2. Furthermore, cluster 2 was characterized by a worse physical and psychosocial health, a higher pain severity and a larger pain interference in daily life. The results emphasize that non-musculoskeletal symptoms are an important complication of EDS-HT, as the number of these complaints was found to be a significant predictor for both functional health status (SIP) and pain experience (MPI). In conclusion, this study confirms that EDS-HT is a heterogeneous entity and encourages the clinician to be more aware of the large variety of EDS-HT symptoms, in order to improve disease recognition and to establish more tailored treatment strategies.

1. Introduction

The Ehlers-Danlos syndrome (EDS) comprises a heterogeneous group of heritable connective tissue disorders, characterized by an abnormal biosynthesis or secretion of fibrillar collagens (Beighton, De Paepe, Steinmann, Tsipouras, & Wenstrup, 1998). The three main clinical manifestations of EDS are joint hypermobility, skin laxity and tissue fragility (Beighton et al., 1998). Patients are currently classified according to the Villefranche criteria into six major types (Beighton et al., 1998) of which the hypermobility type (EDS-HT) is most prevalent (Levy, 2004). In this type, joint hypermobility and recurrent joint dislocations are typically present from childhood on, which in combination with muscle hypotonia may cause

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http://dx.doi.org/10.1016/j.ridd.2012.11.018

a delay in motor development. Later in life, hypermobility often leads to chronic widespread pain and severe physical disability (Castori et al., 2010).

Although at first glance EDS-HT may appear to be a chronic musculoskeletal disorder, it is also associated with 'non'-musculoskeletal problems such as fatigue, orthostatic intolerance and gastrointestinal complaints (Castori et al., 2010; Rowe et al., 1999; Voermans, Knoop, Bleijenberg, & van Engelen, 2010a; Voermans et al., 2010b). These systemic complaints have not been extensively studied and often receive little attention in clinical practice (Grahame, 2008). However, because EDS-HT is a connective tissue disorder rather than a musculoskeletal disorder, the clinician should be aware that patients may present with a large variety of symptoms ranging from the musculoskeletal system to far beyond (Castori et al., 2010; Grahame, 2008; Maeland, Assmus, & Berglund, 2011). This variability in the clinical picture likely contributes to the difficult recognition and diagnosis of the condition. The lack of a correct diagnosis has been shown to severely affect the functionality and quality of life of the patients, usually in terms of excessive financial and time expense, superfluous investigations, wrong therapies, delay of appropriate treatment, and worsening of the disease state (Castori et al., 2010).

Therefore, detailed information on the clinical variability in EDS-HT may be of help in the recognition of the disorder in primary care. This need has been clearly expressed by an expert group meeting in Helsinki, which requested the identification of the range of clinical symptoms associated with EDS-HT and asked for the definition of subsets of patients (Remvig et al., 2011). According to these experts, the current diagnostic criteria insufficiently address the variability seen among patients and lack information regarding features that have recently been recognized.

In addition, investigating clinical variability and identifying subsets of patients in the EDS-HT population may also aid in establishing a more tailored treatment program. Current treatment is often experienced as insufficient and unsatisfactory (Rombaut et al., 2011a). One possible reason may be that treatment for EDS-HT is still poorly defined, and consequently is rather general and vague (Rombaut et al., 2011a). Identification of subsets of patients may lead to the development of more specified treatment strategies for each subgroup. Second, treatment may also be experienced as insufficient because nowadays it is mostly aimed at controlling the typical musculoskeletal symptoms (Rombaut et al., 2011a). The non-musculoskeletal complications of EDS-HT are often overlooked and remain untreated, as they are less obvious compared to the overt joint hypermobility. Consequently, identification of the full range of symptoms may lead to more integrated treatment strategies.

Therefore, the main objective of the present study is to describe the clinical heterogeneity in EDS-HT, with special attention for the presence of non-musculoskeletal symptoms, and to investigate whether subgroups with distinct symptom profiles can be identified in a large patient sample. The secondary objective is to assess whether the subgroup differences are also reflected as disparity in impairment, pain experience, and medication use.

2. Methods

2.1. Participants

Seventy-eight patients, 70 women and 8 men (mean age 40.3 ± 12.6), participated in the study. Patient selection was performed at the Center for Medical Genetics of the Ghent University Hospital. The participants were diagnosed with EDS-HT according to the Revised Villefranche criteria. All patients fulfilled the presence of the 2 major criteria, including generalized joint hypermobility and skin hyperextensibility or skin fragility, and the presence of at least two minor criteria, including recurrent joint dislocations, and/or chronic musculoskeletal pain, and/or a positive family history (Beighton et al., 1998). Before participating in the study, the medical health records of the participants were screened by the treating practitioner (author F.M.) in order to avoid co- and multimorbidity. Patients with another disease in addition to EDS (*e.g.* diabetes, multiple sclerosis, *etc.*) were excluded from the study. Also, pregnant women were not included in the study group. After a routine follow-up consultation at the Center for Medical Genetics, 80 consecutive eligible patients received written information about the purpose of the study. Those who agreed to participate ($n = 78$) signed an informed consent and received the questionnaires with a stamped return envelope enclosed. All questionnaires were returned complete and were used in the data analysis. The research design was reviewed and approved by the local Ethics Committee of the Ghent University Hospital.

2.2. Evaluation

2.2.1. General characteristics

Demographic data regarding gender, age, civil state, employment status, educational level and number of children were collected.

2.2.2. Symptom profile

Information regarding EDS symptoms was collected using a self-reported questionnaire enquiring about symptoms experienced on a regular basis due to EDS (Rombaut, Malfait, Cools, De Paepe, & Calders, 2010). Afterwards, similar symptoms were combined for analysis, in accordance with the method used by Hakim and Grahame (2004). For instance, 'feeling lightheaded after standing-up' or 'feeling faint after standing-up' were considered synonymous with presyncope and were not treated as mutually exclusive. Three researchers, of which 2 physiotherapists (authors I.DW. and L.R.) and one clinician (author F.M.) independently labeled the complaints of each patient. Afterwards, their results were compared and discussed.