Chronic fatigue syndrome is commonly diagnosed in patients with Ehlers-Danlos syndrome hypermobility type/joint hypermobility syndrome

Sirs

Ehlers-Danlos syndrome (EDS) hypermobility type (EDS-HT), now corresponding to the joint hypermobility syndrome (JHS), is an apparently rare, but largely underdiagnosed inherited rheumatologic condition characterised by joint hypermobility (JHM) and related musculoskeletal, pelvic, dysautonomic and gastrointestinal features (1). In addition, recent studies highlight that fatigue and chronic pain are relevant and probably the most disabling features in EDS-HT/JHS (2-3). Chronic fatigue syndrome (CFS) is a relatively common condition diagnosed by the combination of long-lasting fatigue and a series of additional features (4). Marked clinical variability has been recognised in CFS and, at least, one subgroup of patients has been identified by the presence of widespread musculoskeletal pain (5). Interestingly, an increased rate of JHM/EDS have been reported in CFS patients (6-9). Conversely, no study has systematically investigated the frequency of CFS in EDS-HT/JHS.

From a total of 72 patients with various forms of EDS, 46 individuals were selected according to published diagnostic criteria for both EDS-HT (Villefranche criteria) and JHS (Brighton criteria) (1). According to the last conceptual framework for CFS (4), physical examination was integrated with body mass index calculation and palpation for tender lymph nodes. Laboratory investigations included complete blood count, erythrocyte sedimentation rate, serum levels of alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, blood urea nitrogen, electrolytes, creatinine, thyroid-stimulating hormone, ANA, rheumatoid factor and urinalysis. Clinical records were reviewed for major primary depressive disorders with psychotic or melancholic features, bipolar affective disorders, schizophrenia, dementia, anorexia and bulimia nervosa, sleep apnea, narcolepsy, iatrogenic conditions secondary to side effects of prolonged medications, and alcohol or other substance abuse. All patients were screened for the published CFS criteria (5). Frequencies of all CFS features were compared with a sex- and age-matched control group of 95 individuals (Table I). Overall, 82.6% (38/46) of the EDS-HT/JHS patients met the diagnostic criteria for CFS. Among them, eleven (28.5%) showed 6 additional features, sixteen (43%) 5 and eleven (28.5%) 4. Within the EDS-HT group, differences between females (33 with CFS, 5 without CFS) and males (6 with CFS, 2 without CFS) were not statistically significant (p=0.39).

Table I. Features of chronic fatigue syndrome in EDS-HT patients and the control group.

Features	EDS-HT patients (n=46)	Control group (n=95)	p-value
Sex ratio (female/male)	39/7	72/23	NS
Age at evaluation	8-58	28-45	NS
Body mass index	14.64-30.85	–	–
Positive family history	20/45 (45.4%)	–	–
Congenital contortionism	41/46 (89.1%)	–	–
Motor delay/clumsiness	10/45 (22.2%)	–	–
Residual joint hypermobility (Beighton score ≥4)	34/45 (75.5%)	–	–
Recurrent (≥3) joint dislocations	34/46 (73.9%)	–	–
Recurrent (≥3) soft tissue lesions	18/46 (39.1%)	–	–
Velvety/smooth skin	35/46 (76.1%)	–	–
Hyperextensible skin	12/46 (26.1%)	–	–
Easy bruising	31/46 (67.4%)	–	–
Eyelid ptosis	17/46 (36.9%)	–	–
Varicose veins/hemorrhoids	9/46 (19.6%)	–	–
Hernias	2/46 (4.3%)	–	–
Uterine/vescical/rectal prolapse	5/46\(10.9%)	–	–
Chronic (>6 months) and disabling fatigue	38/46 (82.6%)	8/95 (8.4%)	**<0.01**
Post-exertional malaise	37/46 (80.4%)	9/95 (9.4%)	**<0.01**
Unrefreshing sleep	31/46 (67.4%)	41/95 (43.5%)	NS
Impaired memory/concentration	27/46 (58.7%)	35/95 (36.84%)	NS
Multi-joint pain	36/46 (78.5%)	24/95 (25.26%)	**<0.01**
Recurrent headaches	31/46 (67.4%)	26/95 (27.36%)	**<0.01**
Muscle pain	37/46 (80.4%)	14/95 (14.73%)	**<0.01**
Sore throat	2/46 (4.3%)	8/95 (8.42%)	NS
Tender cervical/axillary glands	1/46 (2.2%)	7/95 (7.36%)	NS
Chronic and disabling fatigue plus 4 or more additional features	38/46 (82.6%)	2/95 (2.1%)	**<0.01**

N: number; NS: not significant.

This study demonstrated that most EDS-HT/JHS patients met diagnostic criteria for CFS, with similar rates between sexes. As both EDS-HT/JHS and CFS are more common in females, one could expect a predominance of CFS in EDS-HT/JHS females, but this is not the case in our sample. This could represent a bias related to the small sample size and/or to the fact that, in addition to joint complications directly related to joint laxity, some CFS manifestations (such as muscle/joint pain) are equally common reasons of referral to physicians. In other words, while the downward spiral determining symptom development and worsening in EDS-HT/JHS is facilitated in females, the consequences of these symptoms in terms of health perception and quality of life are essentially the same among sexes.

Among the 8 CFS diagnostic criteria, 4 (*i.e.* unrefreshing sleep, impaired memory/concentration, sore throat, tender lymph nodes) are not more common in our patients' sample. Concerning sleep and memory/concentration dysfunction, this evidence is apparently in contrast with the common knowledge in EDS-HT/JHS and the lack of a statistically significant support to this concept is very probably linked to the paucity of investigated subjects and/or the lack of administration of specific questionnaires. Furthermore, tender lymph nodes and sore throat were only rarely reported in our sample and always unlinked to the other diagnostic criteria. This evidence may mirror a dichotomy among the diagnostic criteria of CFS, where the first 6 are related to a primary dysfunction of the musculoskeletal system, while the other 2 are more linked to an underlying impairment of the immune system (Table I). Accordingly, EDS-HT/JHS patients may represent a significant and probably underestimated subgroup of CFS patients, in whom JHM (either evident or anamnestic) indicates a high rate of musculoskeletal complaints most likely related to the underlying dysautonomia (10), compared to the relative paucity of signs of chronic inflammation. This hypothesis is strengthened by the well-known difficulty in recognising EDS-HT/JHS, as this diagnosis cannot be confirmed by laboratory testing. Therefore, we underline once more the need to search for JHM and other EDS-HT/JHS features (*i.e.* Brighton/Villefranche criteria) in all patients presenting with CFS and severe musculoskeletal complaints.

Acknowledgements

The authors thank all participating patients for their enthusiasm and confidence in our efforts in ameliorating their quality of life.

M. CASTORI, *MD*[1]
C. CELLETTI, *MD*[2]
F. CAMEROTA, *MD*[2]
P. GRAMMATICO, *BSC*, *PhD*[1]

[1]Medical Genetics, Department of Molecular Medicine, Sapienza University, San Camillo-Forlanini Hospital, Rome, Italy;
[2]Physical Medicine and Rehabilitation, Department of Orthopaedics, Sapienza University, Umberto I Hospital, Rome, Italy.

Address correspondence to: Marco Castori, MD, Medical Genetics, Department of Molecular Medicine, Sapienza University, S. Camillo-Forlanini Hospitalm Circonvallazione Gianicolense, 87 I-00152 Rome, Italy
E-mail: mcastori@scamilloforlanini.rm.it
Competing interests: none declared.

References

1. GRAHAME R: What is the joint hypermobility syndrome? JHS from the cradle to the grave. *In* HAKIM AJ, KEER R, GRAHAME R (Eds): Hypermobility, Fibromyalgia and Chronic Pain. Edimburgh, United Kingdom, Chirchill Livingstone Elsevier, 2010: 61-68.
2. VOERMANS NC, KNOOP H, VAN DE KAMP N, HAMEL BC, BLEIJENBERG G, VAN ENGELEN BG: Fatigue is a frequent and clinically relevant problem in Ehlers-Danlos syndrome. *Semin Arthritis Rheum* 2010; 40: 267-74.
3. VOERMANS NC, KNOOP H, BLEIJENBERG G, VAN ENGELEN BG: Pain in ehlers-danlos syndrome is common, severe, and associated with functional impairment. *J Pain Symptom Manage* 2010; 40: 370-8.
4. FUKUDA K, STRAUS SE, HICKIE I, SHARPE MC, DOBBINS JG, KOMAROFF A: The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994; 121: 953-9.
5. NIJS J, MEEUS M, DE MEIRLEIR K: Chronic musculoskeletal pain in chronic fatigue syndrome: recent developments and therapeutic implications. *Man Ther* 2006; 11: 187-91.
6. ROWE PC, BARRON DF, CALKINS H, MAUMENEE IH, TONG PY, GERAGHTY MT: Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J Pediatr* 1999; 135: 494-9.
7. BARRON DF, COHEN BA, GERAGHTY MT, VIOLAND R, ROWE PC: Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls. *J Pediatr* 2002; 141: 421-5.
8. NIJS J, DE MEIRLEIR K, TRUYEN S: Hypermobility in patients with chronic fatigue syndrome: preliminary observations. *Journal of Musculoskeletal Pain* 2004; 12: 9-17.
9. NIJS J, AERTS A, DE MEIRLEIR K: Generalized joint hypermobility is more common in chronic fatigue syndrome than in healthy control subjects. *J Manipulative Physiol Ther* 2006; 29: 32-9.
10. BRAVO JF, SANHUEZA G, HAKIM AJ: Cardiovascular autonomic dysfunction and chronic fatigue in fibromyalgia and joint hypermobility sindrome. *In* HAKIM AJ, KEER R, GRAHAME R (Eds): Hypermobility, fibromyalgia and chronic pain. *Oxford, Churchill Livingstone*, 2010: 69-82.