

NFC and median duration of cGvHD before NFC was much shorter in their patient group (3 vs 30 months). Fleming *et al.* [4] noted areas of microvascular proliferations in some cGvHD biopsies, especially in those with a lichenoid histological picture. We do not know whether the NFC abnormalities described by Akay *et al.* were different between patients with lichenoid changes (nine in Akay's report) or not, but we did not observe any NFC abnormalities in our patients with lichenoid changes. Furthermore, these authors used dermatoscopy—a method that showed inferior reliability in patients with SSc compared with standard NFC [7]. This fact may have additionally contributed to the different interpretation of the capillary morphology. On the other hand, our findings support those of Fleming *et al.* [4] who could demonstrate by histopathology only slight alterations in superficial dermal microvessels in cGvHD in contrast to patients with SSc, in whom capillaries were significantly reduced in number, showed fewer canonical endothelial markers and no microvascular endothelial proliferation.

In summary, our results further support the hypothesis that cGvHD of the skin and SSc are two similar-looking phenomena of skin fibrosis, but with a different pathophysiology, and therefore may need different therapeutic approaches. Thus, cGvHD patients and pathological findings on NFC may represent a different group and should be carefully evaluated for new-onset collagenosis.

#### Rheumatology key message

- Patients with cGvHD of the skin after HCST present normal nail-fold capillary findings.

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## References

- 1 Aschwanden M, Daikeler T, Jaeger KA *et al.* Rapid improvement of nailfold capillaroscopy after intense immunosuppression for systemic sclerosis and mixed connective tissue disease. *Ann Rheum Dis* 2008;67:1057–9.
- 2 Gutierrez M, De Angelis R, Bertolazzi C, Grassi W. Capillaroscopic scleroderma-like pattern in patients without connective tissue disorders. *Rheumatology* 2010;49:1994–6.

- 3 Biedermann BC, Sahner S, Gregor M *et al.* Endothelial injury mediated by cytotoxic T lymphocytes and loss of microvessels in chronic graft versus host disease. *Lancet* 2002;359:2078–83.
- 4 Fleming JN, Shulman HM, Nash AR *et al.* Cutaneous chronic graft-versus-host disease does not have the abnormal endothelial phenotype or vascular rarefaction characteristic of systemic sclerosis. *PLoS One* 2009;4:e6203.
- 5 Filipovich AH, Weisdorf D, Pavletic S *et al.* National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant* 2005;11:945–56.
- 6 Akay BN, Sanli H, Topcuoglu P, Arat M, Akyol A. Nailfold capillary abnormalities are prevalent in scleroderma-like graft-versus-host disease and readily detected with dermatoscopy. *Br J Dermatol* 2010;162:1076–82.
- 7 Baron M, Bell M, Bookman A *et al.* Office capillaroscopy in systemic sclerosis. *Clin Rheumatol* 2007;26:1268–74.

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### Need for a consensus on the methods by which to measure joint mobility and the definition of norms for hypermobility that reflect age, gender and ethnic-dependent variation: is revision of criteria for joint hypermobility syndrome and Ehlers-Danlos syndrome hypermobility type indicated?

SIR, Joint mobility is a continuous trait that varies with joint location and is strongly influenced by age, gender and ethnic origin. Variation in joint mobility probably begins *in utero* and can be expressed, often most dramatically, in individuals with heritable syndromes, such as forms of Ehlers-Danlos syndrome (EDS) and various conditions in which joint contracture is a conspicuous feature. In individuals with these disorders, the diagnosis generally depends on the sum of the different features of the condition, in a sense the gestalt of the presentation. In general, the ability to formulate these diagnoses depends in large part on the experience of the clinician and awareness of the classical descriptions of the syndromes.

Individuals with syndromic forms of abnormalities in joint mobility tend to fall into the diagnostic realm of the geneticist, paediatrician, rheumatologist or other specialists, depending on the national preferences for referral. Their clinical care is often assumed by rheumatologists and physical therapists. A second and much larger group of individuals occupies the attention of both rheumatologists and geneticists—those who have joint mobility that seems out of the usual range (usually increased) at some point in their lives. They may have acute or chronic subluxation, may have joint-related pain that seems out of proportion to clinical signs and more often than not are female. In part, because of the

**TABLE 1** Comparison of clinical signs in criteria sets for EDS and BJHS

EDS classical type	EDS hypermobile type	BJHS
Major criteria		
Skin hyperextensibility	Hyperextensibility and/or smooth velvety skin	Beighton score $\geq$ 4/9
Widened atrophic scars	Beighton score $\geq$ 5/9	Arthralgia for >3 months
Beighton score $\geq$ 5/9		
Minor criteria		
Smooth, velvety skin	Recurring joint dislocations	Dislocation/subluxation
Dislocations/subluxations	Chronic joint/limb pain	Skin hyperextensibility, or papyraceous scarring
Positive family history	Positive family history	Positive family history

dissociation of signs and symptoms, this group of individuals with joint hypermobility, tendency to subluxation and joint pain has proved frustrating to clinicians and to the affected individuals themselves and has led to alienation from the medical system and increased demands for recognition and the creation of meaningful, shared and useful formats for diagnosis and treatment.

The two major specialties concerned with efforts to understand this group of hypermobile and pain-suffering individuals have been rheumatologists and geneticists who have developed similar approaches in parallel. Rheumatologists have developed an approach to diagnosis embedded in the concept of joint hypermobility syndrome, which focuses on mobility and duration of pain. Geneticists have approached the group from the perspective of a dominantly inherited form of EDS, hypermobile type, in which the focus is on joint mobility and mode of inheritance.

The two approaches to diagnosis and evaluation, Brighton criteria for benign joint hypermobility syndrome (BJHS) [1] and the Villefranche criteria [2] for the diagnosis of different forms of EDS, use similar although not overlapping signs and symptoms to identify individuals in whom joint hypermobility is one of the overriding themes (Table 1). Neither deals effectively with the extent of variability seen among these individuals.

It is striking that neither the literature nor the two sets of criteria describe precisely how to perform the clinical tests used to make the clinical diagnoses. Consequently, considerable variation in test performance is presented in scientific publications, in textbooks and on the web, thereby increasing the variations in diagnostic results.

Developed more than a decade ago, neither of these two formulations for the diagnosis of entities in which joint hypermobility is a prominent feature mentioned some of the striking features that have since been recognized: the predominance of females in the affected group, the presence of signs and symptoms of dysautonomia in an apparent subset [3], the emergence of unexplained pain that did not match the overt findings (Brighton criteria ranks this an important facet of the diagnosis), gastrointestinal involvement [4] and the association of other psychological features [5]. Nor did either group consider the issues of aetiological heterogeneity or how to

standardize clinical evaluation [6–9] in establishing diagnostic criteria.

Given these considerations, the faculty agreed that there is an urgent need to develop a standard protocol for the assessment of joint mobility taking age, gender and ethnic origin into consideration. Further, the members agreed that identification of the range of associated clinical aspects needed to be developed, that thought be given to the extent to which subsets could be defined and that integrated treatment strategies that reflected the full range of variables need to be developed and implemented.

Finally, the members of the faculty recognized that this group of individuals with joint hypermobility and a range of associated clinical aspects present challenges to diagnosis and management that often put barriers between the practitioner and the individuals to be assessed and cared for. The development of a better way to understand these disorders and their associated findings should convert the current difficulties and scepticism into a more robust interaction that leads to precise diagnosis, recognition of heterogeneity within the group and creation of targeted and effective therapies.

The faculty, thus, urges that national societies within clinically relevant specialties form an International Committee to standardize the clinical assessment of joint mobility, to determine age, gender and ethnic standards for joint mobility, to examine the concept of heterogeneity within the group of individuals with non-syndromic joint hypermobility and to determine the features that contribute to that heterogeneity and develop or identify the strategies to measure the elements that contribute to this heterogeneity.

#### Rheumatology key message

- Revision of criteria for joint hypermobility syndrome and EDS hypermobility type is urgently needed.

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## References

- Grahame R, Bird HA, Child A. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). *J Rheumatol* 2000;27: 1777–9.
- Beighton P, de Pape A, Steinmann A, Tsipouras P, Wenstrup R. Ehlers-Danlos syndromes: revised Nosology, Villefranche 1997. *Am J Med Genet* 1998;77: 31–7.
- Hakim AJ, Grahame R. Non-musculoskeletal symptoms in joint hypermobility syndrome. Indirect evidence for autonomic dysfunction? *Rheumatology* 2004;43: 1194–5.
- Zarate N, Farmer AD, Grahame R *et al*. Unexplained gastrointestinal symptoms and joint hypermobility: is connective tissue the missing link? *Neurogastroenterol Motil* 2010;22:252–62.
- Bulbena A, Agullo A, Pailhez G *et al*. Is joint hypermobility related to anxiety in a nonclinical population also? *Psychosomatics* 2004;45:432–7.
- Bulbena A, Duro JC, Porta M, Faus S, Vallescar R, Martin-Santos R. Clinical assessment of hypermobility of joints: assembling criteria. *J Rheumatol* 1992;19: 115–22.
- Farmer AD, Douthwaite H, Gardiner S, Aziz Q, Grahame R. A novel in vivo skin extensibility test for joint hypermobility. *J Rheumatol* 2010;37:1513–8.
- Juul-Kristensen B, Røgind H, Jensen D, Remvig L. Inter-examiner reproducibility of tests and criteria for generalised joint hypermobility and benign joint hypermobility syndrome. *Rheumatology* 2007;46: 1835–41.
- Remvig L, Duhn P, Ullman S *et al*. Skin signs in Ehlers-Danlos syndrome: clinical tests and para-clinical methods. *Scand J Rheumatol* 2010;39: 511–7.

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## A Japanese case of familial Mediterranean fever presenting diffuse bone marrow uptake of FDG-PET and high levels of neutrophil membrane CD64 expression

SIR, FMF is a rare inflammatory disease characterized by recurrent attacks of fever and inflammation. Even though some useful diagnostic criteria have been proposed, useful imaging methods or haematological markers for the diagnosis or follow-up of FMF have not been established. We experienced a case of a 46-year-old woman with FMF presenting diffuse bone marrow uptake of [<sup>18</sup>F] fluoro-deoxy glucose (FDG) and high levels of polymorphonuclear neutrophil (PMN) membrane CD64 expression.

A 46-year-old Japanese female was admitted to our hospital because of chest pain and fever of undetermined origin (FUO). She had been suffering from a periodic fever since she was 18-years old. [<sup>18</sup>F]FDG-PET was performed, revealing diffuse bone marrow uptake of [<sup>18</sup>F]FDG (Fig. 1). In the laboratory findings of haematology and biochemistry at the time of admission, there were no abnormalities except for elevated ESR and elevated levels of CRP (ESR 51 mm/h, CRP 6.54 mg/dl). Tests for ANAs, ANCAs and RF were negative. A peripheral blood smear revealed no abnormalities. Serum M-protein was not detected by immunofixation. Since we suspected FMF based on these findings, we performed the sequencing of all 10 exons of the *MEFV* gene and detected a heterozygous mutation (GAG to AAG) in codon 84 of exon 1 of the *MEFV* gene that resulted in a substitution of lysine for glutamic acid (E84K). In light of these findings, we initiated daily colchicine treatment (1.0 mg/day), and the patient's clinical manifestation rapidly improved. FMF was diagnosed according to clinical criteria for the diagnosis in combination with a classification tree format [1].

The expression of CD64 on PMNs in healthy subjects, before and after treatment, was measured by flow cytometry using a Coulter Epics XL flow cytometer (Beckman Coulter, Inc. Brea, CA, USA) using Expo32 ADC analysis software (Beckman Coulter). Before the colchicine treatment, the patient's mean fluorescence intensity (MFI) of CD64 on PMNs was significantly increased (MFI: 12.4) compared with those of healthy subjects (MFI: 1.2). Colchicine treatment (1.0 mg/day) down-regulated the increased CD64 expression, but expression was higher than in healthy subjects (MFI: 7.4).

FMF is prevalent among populations surrounding the Mediterranean Sea. However, more cases have been reported in countries not related to this area, including Japan. In countries where FMF is rare, a clinical diagnosis of FMF may not be easy, and the role of genetic testing is crucial. More recently, Tomiyama *et al*. [2] reported a new *MEFV* mutation, E84K, in a Japanese FMF patient.

Hyperfunction of PMNs is a characteristic of FMF. CD64 (FCγR1), a factor crystallizable (FC) receptor for immunoglobulin G (IgG), plays a role in antibody-dependent cytotoxicity, clearance of ICs and phagocytosis of targets