Clin Rheumatol (2015) 34:1613–1619
DOI 10.1007/s10067-014-2610-6

ORIGINAL ARTICLE

Is pain the only symptom in patients with benign joint hypermobility syndrome?

İlknur Albayrak · Halim Yilmaz · Halil Ekrem Akkurt · Ali Salli · Gülten Karaca

Received: 10 March 2014 / Revised: 30 March 2014 / Accepted: 2 April 2014 / Published online: 18 April 2014

Abstract The aims of this study were to evaluate pain, depression level, fatigue, sleep, and quality of life (QoL) among patients with benign joint hypermobility syndrome (BJHS) and to compare their results with those of healthy controls. The study involved 115 patients and 114 healthy volunteers. Pain level was rated using visual analogue scale (VAS) for all patients. Depression level, fatigue, sleep quality, and QoL of all the participants were evaluated by the Beck Depression Inventory (BDI), the Checklist Individual Strength (CIS), the Pittsburgh Sleep Quality Index (PSQI), and the Short Form-36 (SF-36), respectively. VAS value was 6.29±0.94 in the patient group. Comparison of two groups showed that there were statistically significant differences between the patient group and the control group with respect to BDI, total CIS, PSQI scores, SF-36 subscales (physical function, role physical, bodily pain, general health, role emotional, and mental health), and mental component summary ($p<0.001$). While pain is the predominant symptom among BJHS patients, depression, fatigue, impaired sleep, and QoL also commonly occur. Thus, all of these components should be taken into account when assessing patients with BJHS.

Keywords Benign joint hypermobility syndrome · Depression level · Fatigue · Quality of life · Sleep quality

İ. Albayrak (✉)
Department of Physical Medicine and Rehabilitation, Medical School of Selcuk University, Konya, Turkey
e-mail: ilknurftr@gmail.com

H. Yilmaz · H. E. Akkurt · G. Karaca
Department of Physical Medicine and Rehabilitation, Konya Education and Research Hospital, Konya, Turkey

A. Salli
Department of Physical Medicine and Rehabilitation, Meram Medical School of Necmettin Erbakan University, Konya, Turkey

Introduction

Hypermobility refers to an increased range of motion in one or more joints. Benign joint hypermobility syndrome (BJHS) is a disorder associated with musculoskeletal symptoms affecting hypermobile individuals without any systemic rheumatic disease [1]. Many authorities consider BJHS to be synonymous with Ehlers–Danlos syndrome (EDS) hypermobility type, formerly known as EDS type-3 [2, 3]. Hypermobility occurs at a rate of 4–13 % in the general population, and its incidence decreases with advancing age [4]. Joint hypermobility is more common in females compared to males, with symptomatic disease affecting 5 % of the female population and 0.6 % of the male population [5].

BJHS results from an abnormality of the structure of type-1 collagen, which is the most abundant collagen in the human body [4]. Type-1 collagen is mostly found in tendons, ligaments, joint capsules, skin, and bone. The altered structure of collagen in BJHS results in less stiffness, more flexibility, and hypermobility in the aforementioned regions.

Pain is one of the major symptoms of BJHS. Several factors are implicated in BJHS-related pain. Pain may be the end result of a decrease in the sense of joint position that causes joints to become more susceptible to injury. Abnormal stress and strain result in acute injury of ligaments and soft tissue, injuries stemming from the overuse and joint instability [6]. Arthralgia and osteoarthritis may occur in the long term due to excessive movement of the joints [6]. Eventually, chronic pain develops with repeated episodes and increased severity of pain [7]. Sleep quality, social relationships, physical activities, and quality of life (QoL) are adversely affected in the presence of persistent pain. In the end, psychological problems occur. There is an increased incidence of psychiatric symptoms, including depression, anxiety, and panic disorders, among BJHS patients due to years of suffering from side effects of the condition, such as

long-standing joint pain, impaired sleep quality, and fatigue [8, 9]. In addition, pain, fatigue, and associated symptoms of low energy and weakness are prevalent in BJHS and adversely affect QoL [10–12].

Previous studies have assessed the aforementioned common systemic symptoms, such as pain, increased incidence of depression, fatigue, sleep disorders, and impaired QoL in BJHS patients separately, but none has examined all these symptoms collectively in the same patient group [6–12]. In this study, we aimed to assess pain, depression, fatigue, sleep, and QoL in a group of BJHS patients to determine the associations, if any, between these factors and to compare the results with a group of healthy controls.

Materials and methods

Subjects

This study was conducted at the physical medicine and rehabilitation department in Konya Research and Educational Hospital from April 2013 to December 2013. A total of 115 patients aged between 18 and 50 years who had been diagnosed with BJHS and severe pain with VAS score of 3 or greater were enrolled into the patient group. The patients were initially evaluated according to the Beighton score for BJHS [13] (Table 1). Then, the patients were diagnosed with BJHS according to the Brighton criteria (Table 2) [14]. The patients with BJHS were consecutively enrolled into the study according to the inclusion and exclusion criteria. The control group consisted of 114 age-matched healthy volunteers meeting the same inclusion and exclusion criteria as the BJHS group but had no BJHS or pain.

The patients younger than 18 years and older than 50 years, and with a pain severity score equal to or greater than 8 points as assessed by the VAS, those with a fracture leading to joint pain and any pathological features such as joint dislocation, acute strain, or sprain and with disorders giving rise to hypermobility other than BJHS (collagen tissue disorders such as Marfan syndrome, EDS other than type-3, metabolic disorders such as homocysteinuria, and genetic disorders such as Down's syndrome), those on the use of analgesics or non-steroid anti-inflammatory drugs in the previous week and antidepressant or anxiolytic drugs, those with an inflammatory rheumatic condition, hypothyroidism, or anaemia, and those with pregnancy or with diminished cognitive function who were unable to complete the study, were excluded out of the study. An approval from the local ethics committee was obtained. All the participants were informed about the study, and written consent was obtained from all the participants.

Table 1 Beighton 9-point scoring system

Maneuver	Right	Left
Ability to passively dorsiflex the 5th metacarpophalangeal joint to 90°	1 point	1 point
Ability to appose the thumb to the volar aspect of the ipsilateral forearm	1 point	1 point
Ability to hyperextend the elbow joint to beyond 10°	1 point	1 point
Ability to hyperextend the knee joint to beyond 10°	1 point	1 point
Ability to place the hands flat on the floor by bending forward with knees fully extended	1 point	
Total	9 of 9 points	

Data collection

All the participants completed the questionnaire, which gathered demographic data (age, gender, body mass index, marital status, education level and occupation). Information on the location of the most painful joint (neck, low back, back, wrist, ankle or knee), and the duration of the pain was obtained from the patient group by a researcher at the first office visit [15]. The participants were requested not to exercise 24 hours before the second visit, so as not to influence the VAS, Checklist Individual Strength (CIS), and Pittsburgh Sleep Quality Index (PSQI) scores.

Table 2 Brighton criteria-diagnostic criteria for hypermobility syndrome

Major criteria
1. A Beighton score of 4/9 or greater
2. Arthralgia for longer than 3 months in four or more joints.
Minor criteria
1. A Beighton score of 1, 2, or 3/9 (0, 1, 2, or 3 if aged 50+).
2. Arthralgia (for 3 months or longer) in one to three joints or back pain for (for 3 months or longer)
spondylosis, spondylolysis, or spondylolisthesis.
3. Dislocation/subluxation in more than one joint or in one joint on more than one occasion.
4. Three or more soft tissue lesions (e.g., epicondylitis, tenosynovitis, and bursitis).
5. Marfanoid habitus (tall, slim, span/height ratio>1.03; upper/lower segment ratio<0.89) and
arachnodactyly (positive steinberg/wrist signs).
6. Abnormal skin striae, hyperextensibility, thin skin, or abnormal scarring.
7. Ocular signs, drooping eyelids or myopia or antimongoloid slant.
8. Varicose veins or hernia or uterine/rectal prolapse.

BJHS is diagnosed in the presence of two major criteria or one major and two minor criteria, or four minor criteria. Two minor criteria will suffice where there is an unequivocally affected first-degree relative. BJHS is excluded by the presence of Marfan or Ehlers–Danlos syndromes (EDS) other than the EDS hypermobility type (formerly EDS III)

During the second visit, the pain level of all the patients was rated using the VAS. The depression levels, fatigue, sleep quality and QoL of all the participants were evaluated by the Beck Depression Inventory (BDI), CIS, PSQI, and Short Form-36 (SF-36) questionnaire, respectively. These instruments were recorded by a researcher.

Assessment of pain severity

VAS rates the pain of the individual on a 0–10 scale and is widely used in patients with hypermobility [16, 17]. Pain with movement during the previous week was assessed in the present study.

Assessment of depression level

BDI, which was used to assess the psychological state of the participants, consists of 21 questions. In the BDI, patients are asked to select the most appropriate statement relevant to their condition. Each item includes four statements. These statements are graded in increased order of severity from neutral (0 points) to very severe condition (3 points). The highest possible score is 63 points [18]. The score greater than 17 denotes the presence of depression.

Assessment of fatigue

The multidimensional CIS was used to measure chronic fatigue. It consists of 20 statements, the answers to which are scored on a 7-point Likert scale. The CIS is divided into four dimensions: (1) the subjective experience of fatigue (eight items), (2) reduction in motivation (four items), (3) reduction in activity (three items), and (4) reduction in concentration (five items). A total CIS score is obtained by summing the scores from the four dimensions. Higher scores indicate a higher degree of fatigue, more concentration problems, lower motivation and less activity [19, 20]. The total CIS score was evaluated in the present study.

Assessment of sleep quality

The PSQI, which was used for the assessment of sleep quality, consists of a total of 24 questions, 19 of which are self-rated by the individual, and five of which are answered by the partner or roommate of the individual. The total score ranges between 0 and 21 points. A higher total score indicates worse sleep quality. Based on the total score, sleep quality is rated as good (0–5 points) or poor (6–21 points) [21].

Assessment of QoL

SF-36, which was used to evaluate the QoL, consists of 36 questions, which are employed to obtain scores for eight subscales, including physical function, role physical, role emotional, social functioning, general health, mental health, vitality and bodily pain. Total scores are also obtained for two main domains: a physical component summary (consisting of physical function, role physical, bodily pain and general health subscales) and a mental component summary (consisting of role emotional, social functioning, mental health and vitality). Scores range from 0 (maximum physical limitations) to 100 (optimal physical functioning) points [22].

Statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics version 20. Conformance of the variables to a normal distribution was investigated using visual and analytical methods. Mean (±standard deviation) values were used in the presentation of data. Clinical data conforming to a normal distribution were compared using a Student's t test, and those not conforming to a normal distribution were compared using a Mann–Whitney U test. A Chi-square test was used for comparison of frequencies. To determine linear associations between independent variables, Spearman's rho correlation coefficients were calculated. The statistical significance level was set at $p<0.05$. As for coefficients of correlation, correlations from 0 to 0.25 were considered as 'no correlation,' 0.25 to 0.50 as a 'mild-moderate correlation,' 0.50 to 0.75 as a 'strong correlation,' and between 0.75 and 1.00 as a 'very strong correlation.'

Results

Of 135 study participants, 12 were excluded due to unwillingness to respond to the questionnaire and 8 due to time constraints, which resulted in incomplete responses to the questionnaire. Thus, the study was completed with a total of 229 subjects, including 115 patients and 114 healthy volunteers (control group). The Brighton hypermobility score was 6.73±1 points for the patient group. There were no statistically significant differences between the two groups in age, gender, body mass index, marital status, education level and occupation ($p>0.05$) (Table 3).

The severity and the characteristics of pain are shown in Table 4 for the patient group.

When the two groups were compared, the patient group showed higher scores for BDI (scores above 17 indicated depression), total CIS, PSQI, and SF-36 subscales of bodily pain and general health, whereas the scores for physical function, role physical, role emotional, and mental component summary were found to be lower in the patients, compared to the controls ($p<0.001$) (Table 5).

Table 3 Demographic characteristics of patient and control groups

	Patient group (n=115)	Control group (n=114)	p value
Age, years (mean±SD)	30.17±7.47	31.81±6.86	0.085
Gender			0.69
Female	102 (88.7 %)	99 (86.8 %)	
Male	13 (11.3 %)	15 (13.2 %)	
BMI	25.21±5.02	25.55±4.21	0.57
Marital status			0.118
Married	79 (68.7 %)	87 (76.3 %)	
Single	35 (30.4 %)	23 (20.2 %)	
Divorced	1 (0.9 %)	4 (3.5 %)	
Education level			0.571
No formal education	1 (0.9 %)	0	
Primary school	51 (44.3 %)	49 (43 %)	
Secondary school	13 (11.3 %)	20 (17.5 %)	
High school	23 (20 %)	19 (16.7 %)	
University	27 (23.5 %)	26 (22.8 %)	
Occupation			0.239
Housewife	63 (54.8 %)	52 (45.6 %)	
Officer	37 (32.2 %)	49 (43 %)	
Work requiring physical effort	15 (13 %)	13 (11.4 %)	

SD Standard deviation, *BMI* Body mass index

In the correlation analyses of the data from the BJHS patients, a positive correlation was observed between PSQI, BDI, total CIS and pain scores on the SF-36 (r=0.291, 0.280 and 0.377, respectively); between BDI and pain scores on the SF-36 and total CIS scores (r=0.508 and 0.689, respectively); and between total CIS scores and pain score on the SF-36 (r=0.471). Even so, a negative correlation was found between the PSQI and the physical component summary, mental component summary, role physical and role emotional scores of the SF-36 (r=−0.253, −0.282, −0.338 and −0.281, respectively); between the BDI, physical function, role physical, role emotional, mental health, physical component summary and mental component summary scores of the SF-36 (r=−0.543, −0.428, −0.439, −0.280, −0.399 and −0.423, respectively); and between total CIS score, physical function, role physical, role emotional, physical component summary and mental component summary scores of the SF-36 (r=−0.516, −0.375, −0.317, −0.336 and −0.302, respectively).

Table 4 The severity and characteristics of pain in the patient group

VAS (mean±SD)	6.29±0.94
Duration of pain (months) (mean±SD)	20.95±26.12
Localization of pain	
Neck	23 (20 %)
Low back	37 (32.2 %)
Knee	32 (27.8 %)
Back	6 (5.2 %)
Ankle	5 (4.3 %)
Wrist	10 (8.7 %)
Other joints	2 (1.7 %)

VAS Visual Analogue Scale, *SD* Standard deviation

Discussion

In this study, patients with a diagnosis of BJHS had a higher depression level, increased fatigue, worse sleep quality and impaired QoL in comparison to matched healthy controls. The severity of pain was also greater in the patient group.

BJHS is a systemic multifaceted disorder associated with a plethora of symptoms. The initial complaint is pain, followed by impaired sleep quality and fatigue, which may result in an increased depression level and a diminished QoL over time [7, 8, 10]. However, symptoms other than pain may be overlooked during the examination of BJHS patients unless they are specifically questioned. Indeed, a full recovery is difficult to achieve in these patients by focusing on only the treatment of pain without considering other factors, including their depression level, fatigue, sleep problems, or QoL. Thus, in the present study, pain as well as the depression level, fatigue, sleep problems and QoL, and associations between these parameters were assessed in BJHS patients.

The primary symptom of BJHS is pain, which initially occurs in the form of acute episodes and becomes chronic

Table 5 Comparison of patient and control groups based on BDI, total CIS, PSQI, and SF-36 subscale scores

	Patient group (n=115) mean±SD	Control group (n=114) mean±SD	p value
BDI	14.57±8.12	8.37±6.3	<0.001
Total CIS	83.97±23.66	71.02±26.22	<0.001
PSQI	7.53±2.86	6.14±2.96	<0.001
SF-36			
Physical function	66.73±21.69	77.01±19.71	<0.001
Role physical	38.91±44.57	71.05±35.44	<0.001
Bodily pain	52.69±16.45	25.52±19.19	<0.001
General health	53.08±9.83	48.42±9.73	<0.001
Physical component summary	52.85±13.32	55.5±10.94	>0.05
Vitality	49.65±14.39	48.77±13.29	>0.05
Social function	48.80±17.59	50±14.96	>0.05
Role emotional	41.15±45.74	72.51±34.13	<0.001
Mental health	53.25±11.09	55.85±11.07	>0.05
Mental component summary	48.21±14.53	56.78±12.01	<0.001

SD Standard deviation, *PSQI* Pittsburgh Sleep Quality Index, *BDI* Beck Depression Inventory, *SF-36* Short Form-36, *CIS* Checklist Individual Scale

over time [23]. Patients develop chronic pain as a result of trauma to the joints, muscles and ligaments during daily activities, in combination with excessive joint laxity [7, 14]. One study reported that knee and ankle joints were affected most often by BJHS, whereas another cited the lumbar region as the predominant site of pain [24, 25]. In a study where 273 patients with EDS were evaluated with McGill Pain Questionnaire as to pain severity, it was reported that the existence of chronic pain and the frequency of regular analgesic drug use were higher in EDS patients, and the severity of pain was related to quality of sleep and functional status [26]. As consistent with this study, while the severity of pain evaluated with the VAS was detected to be higher among our patients, the duration of pain complaint was long enough to indicate the presence of chronic pain. In our study, the patients over the age of 50 years at which the prevalence of BJHS decreases and the factors being the reason of other muscle-skeletal pains like osteoarthritis are encountered were not included into the study in order to assess the complaints of pain objectively. Our patients complained about their pain spontaneously, and the pain was a major symptom the patients sought medical help for, unlike fatigue or impaired QoL for which they sought no help. Additionally, the most painful site was lumbar joints followed by knee joints in the present study. Consistent with other studies, the risk of developing pain increased at the site of weight-bearing joints [24, 25]. Thus, these joints in particular should be examined in patients presenting with pain. In addition, a patient education and exercise program should be provided as a prophylactic measure even if the patients currently do not have complaints of pain.

There is an increased incidence of mood disorders, including depression, among patients with BJHS [27, 28]. In a study where 365 university students were evaluated, 39.5 % of all participants were diagnosed with BJHS, and depression was determined to be higher in women diagnosed with BJHS compared to those participants lack of BJHS diagnosis [29]. The incidence of depression is increased in conditions associated with chronic pain, such as BJHS [30]. Eventually, individuals may develop a perception of living a restricted life because of limitations in their daily living and social interactions [31]. They may also experience psychological problems, including a loss of self-esteem, feeling alone and different from others, and find it difficult to explain their situation [31]. Patients may feel alone and think nobody understands their disorder, including their family, after many years of suffering from pain and other physical problems, frequent visits to the doctor, negative thoughts and feelings of uncertainty. All of these contribute to the increased incidence of depression in BJHS patients. We observed a significantly increased level of depression in the patient group. The prevalence of depression in a previous study of patients with chronic pain was 29 versus 44 % in our study [32]. The prevalence of depression is considerably higher in BJHS than in many other chronic disorders. In BJHS patients, it is as important to determine the causes of depression as to detect its presence.

The present study found a strong association between the depression level and fatigue and a moderate association between the depression level and QoL. This finding suggests that one factor may trigger the other, leading to aggravation of BJHS symptoms. However, none of the patients spontaneously reported depression or their QoL. Improvements in the detection and the treatment of depression, as well as fatigue and impaired QoL, can break a vicious cycle.

Although the BJHS patients did not frequently report fatigue and diminished sleep quality, both are common in the disease process [11, 33, 34]. Fatigue occurs not only in the course of BJHS, but is also a frequent symptom in other chronic illnesses, adversely affecting the individual's functional capacity and QoL [35, 36]. In a study in which 68 patients with chronic fatigue syndrome were compared with healthy volunteers as to the incidence of BJHS, the incidence rate of BJHS was seen to be some fivefold higher in the patients (20.6 %) compared to controls (4.3 %) [37]. In other words, a significant correlation is present between fatigue and BJHS. In a study performed with 273 patients with EDS, 77 % were found to suffer from severe fatigue, with parameters influencing fatigue identified as sleep disorders, concentration problems, self-efficacy concerning fatigue, social functions, and pain severity [11]. When we look at the factors associated with low sleep quality, a major cause of fatigue, pain is one of the most important causes of diminished sleep quality, difficulty falling asleep, and staying asleep [36–39]. Studies have demonstrated that resting and improving the sleep quality decreased the severity of fatigue [11]. As consistent with these studies, the BJHS patients in our study had a high level of fatigue and low sleep quality, and fatigue was considered to be associated with diminished sleep quality and decreased QoL. The physical component summary and mental component summary scores of SF-36 were lower in those with increased fatigue and decreased sleep quality. Thus, improvement of sleep quality may result in less fatigue, increased QoL, less severe pain, and a general sense of well-being among BJHS patients, which will shorten the time needed to perform daily activities and increase their physical capacity [11, 40].

Adversely affected by several factors, including musculoskeletal involvement, chronic pain, fatigue, and mood disorders, QoL is considerably important for BJHS patients [10, 34, 26]. QoL is currently assessed using two main domains: the mental and physical component summary scores of the SF-36. In the present study, significantly worse scores for the mental component summary and the physical component summary (including role physical, physical function, bodily pain, and general health) were observed during the assessment of the QoL. An analysis of the association with other parameters to identify contributing factors showed that the QoL worsened with decreased sleep quality and increased levels of fatigue and depression. Currently, therapeutic approaches for many disorders focus on improving the QoL. The QoL of BJHS patients should also be targeted to enable them to become more active and successful in their family and social lives and at work. However, patients never seek medical assistance primarily for diminished QoL. The physician should determine the patient's QoL by questioning his/her psychological state, pain, and sleep quality. Improvement of the QoL may result in decreased levels of depression and fatigue.

The present study has some limitations. First, because the study was conducted in a single center, it cannot be generalized to the whole population, and so the situation has decreased the strength of the study. Second, our study enrolled a predominance of female patients although joint hypermobility is more common encountered in females compared to males as illustrated in the literature [5]. Finally, the present study was designed as cross sectional, not longitudinal. Therefore, further and longitudinal studies are needed to support the results.

Many studies on BJHS have mainly focused on pain because pain is the dominant clinical symptom, and so the patients with BJHS are mostly assessed only for pain. However, as the results of our study suggest, increased depression levels, fatigue and diminished QoL are equally common in such patients. While previous studies have assessed these components separately, our study highlighted the importance of BJHS-related parameters by examining all of them in the same patient group, comparing the results with a matched control, and analysing their interrelations. As a result of this approach, complaints that most patients do not express spontaneously were underlined. In addition, by examining all the complaints in the same patient population, we showed how the presence of one factor may trigger or aggravate another. In conclusion, the assessments of BJHS patients should focus not only on the pain complaint, but also on psychological problems, fatigue, sleep patterns, and QoL. A holistic approach to the assessment including thorough questioning and a multidisciplinary treatment regimen should be preferred based on the results of examination.

Acknowledgments We would like to thank Prof. Funda Levendoglu, M.D. (Department of Physical Medicine and Rehabilitation, Konya Selcuk University School of Medicine) for her valuable insight and contributions to the manuscript.

Conflicts of interest The authors declared that there is no conflict of interest.

References

1. Hakim AJ, Cherkas LF, Grahame R, Spector TD, MacGregor AJ (2004) The genetic epidemiology of joint hypermobility: a population study of female twins. Arthritis Rheum 50(8):2640–2644
2. Grahame R (2001) Time to take hypermobility seriously (in adults and children). Rheumatology 40(5):485–487
3. Tinkle BT, Bird HA, Grahame R, Lavallee M, Levy HP, Sillence D (2009) 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 149A(11):2368–2370
4. Seckin U, Sonel Tur B, Yilmaz O, Yagci I, Bodur H, Arasil T (2005) The prevalence of joint hypermobility among high school students. Rheumatol Int 25(4):260–263

5. Engelbert R, Uiterwaal C, Van de Putte E, Helders P, Sakkers R, Van Tintelen P et al (2004) Pediatric generalized joint hypomobility and musculoskeletal complaints: a new entity? Clinical, biochemical, and osseal characteristics. Pediatrics 113(4):714–719
6. Finsterbush A, Pogrund H (1982) The hypermobility syndrome. Musculoskeletal complaints in 100 consecutive cases of generalized joint hypermobility. Clin Orthop Relat Res 168:124–127
7. Sacheti A, Szemere J, Bernstein B, Tafas T, Schechter N, Tsipouras P (1997) Chronic pain is a manifestation of the Ehlers-Danlos syndrome. J Pain Symptom Manag 14(2):88–93
8. Martín-Santos R, Bulbena A, Porta M, Gago J, Molina L, Duro JC (1998) Association between joint hypermobility syndrome and panic disorder. Am J Psychiatry 155(11):1578–1583
9. Bulbena A, Agulló A, Pailhez G, Martín-Santos R, Porta M, Guitart J et al (2004) Is joint hypermobility related to anxiety in a non-clinical population also? Psychosomatics 45(5):432–437
10. Castori M, Camerota F, Celletti C, Grammatico P, Padua L (2010) Quality of life in the classic and hypermobility types of Ehlers-Danlos syndrome. Ann Neurol 67(1):145–146
11. Voermans NC, Knoop H, van de Kamp N, Hamel BC, Bleijenberg G, van Engelen BG (2010) Fatigue is a frequent and clinically relevant problem in Ehlers-Danlos Syndrome. Semin Arthritis Rheum 40(3): 267–274
12. Kalkman JS, Schillings ML, van der Werf SP, Padberg GW, Zwarts MJ, van Engelen BG et al (2005) Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. J Neurol Neurosurg Psychiatry 76(10):1406–1409
13. Beighton PH, Solomon L, Soskolne CL (1973) Articular mobility in an African population. Ann Rheum Dis 32(5):413–417
14. Grahame R (2000) Pain distress and joint hyperlaxity. Jt Bone Spine 67(3):157–163
15. Simpson MR (2006) Benign joint hypermobility syndrome: Evaluation, diagnosis, and management. J Am Osteopath Assoc 106(9):531–536
16. Ferrell WR, Tennant N, Sturrock RD, Ashton L, Creed G, Brydson G et al (2004) Amelioration of symptoms by enhancement of proprioception in patients with joint hypermobility syndrome. Arthritis Rheum 50(10):3323–3328
17. Ruperto N, Malattia C, Bartoli M, Trail L, Pistorio A, Martini A et al (2004) Functional ability and physical and psychosocial well-being of hypermobile schoolchildren. Clin Exp Rheumatol 22(4):495–498
18. Beck AT, Guth D, Steer RA, Ball R (1997) Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behav Res Ther 35(8):785–791
19. Ergin G, Yildirim Y (2012) A validity and reliability study of the Turkish Checklist Individual Strength (CIS) questionnaire in musculoskeletal physical therapy patients. Physiother Theory Pract 28(8): 624–632
20. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G (1994) Dimensional assessment of chronic fatigue syndrome. J Psychosom Res 38(5):383–392
21. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh sleep quality index (PSQI): a new instrument for psychiatric research and practice. Psychiatry Res 28(2):193–213
22. Stewart JW, Quitkin FM, McGrath PJ, Rabkin JG, Markowitz JS, Tricamo E et al (1988) Social functioning in chronic depression: Effect of 6 weeks of antidepressant treatment. Psychiatry Res 25(2): 213–222
23. Hakim A, Grahame R (2003) Joint hypermobility. Best Pract Res Clin Rheumatol 17(6):989–1004
24. Everman DB, Robin NH (1998) Hypermobility syndrome. Pediatr Rev 19(4):111–117
25. Bravo JF, Wolff C (2006) Clinical study of hereditary disorders of connective tissues in a Chilean population: joint hypermobility syndrome and vascular Ehlers-Danlos syndrome. Arthritis Rheum 54(2): 515–523
26. Voermans NC, Knoop H, Bleijenberg G, van Engelen BG (2010) Pain in EDS is common, severe, and associated with functional impairment. J Pain Symptom Manag 40(3):370–378
27. Lumley MA, Jordan M, Rubenstein R, Tsipouras P, Evans MI (1994) Psychosocial functioning in the Ehlers-Danlos syndrome. Am J Med Genet 53(2):149–152
28. Baeza-Velasco C, Gely-Nargeot MC, Bulbena Vilarrasa A, Bravo JF (2011) Joint hypermobility syndrome: Problems that require psychological intervention. Rheumatol Int 31(9):1131–1136
29. Baeza-Velasco C, Gély-Nargeot MC, Bulbena A, Fénétrier C, Bravo JF (2011) Association between psychopathological factors and joint hypermobility syndrome in a group of undergraduates from a French university. Int J Psychiatry Med 41(2):187–201
30. Fishbain D, Cutler R, RosomoV H, RosomoV R (1997) Chronic pain-associated depression: Antecedent or consequence of chronic pain? A review. Clin J Pain 13(2):116–137
31. Berglund B, Nordstrom G, Lutzen K (2000) Living a restricted life with Ehlers-Danlos syndrome (EDS). Int J Nurs Stud 37(2):111–118
32. Breivik H, Collet B, Ventafridda V, Cohen R, Gallacher A (2006) Survey of chronic pain in Europe: Prevalence, impact of daily life, and treatment. Eur J Pain 10(4):287–333
33. Castori M, Sperduti I, Celletti C, Camerota F, Grammatico P (2011) Symptom and joint mobility progression in the joint hypermobility syndrome (Ehlers-Danlos Syndrome, hypermobility type. Clin Exp Rheumatol 29(6):998–1005
34. Rombaut L, Malfait F, Cools A, De Paepe A, Calders P (2010) Musculoskeletal complaints, physical activity and health-related quality of life among patients with the Ehlers-Danlos syndrome hypermobility type. Disabil Rehabil 32(16):1339–1345
35. Chaudhuri A, Behan PO (2004) Fatigue in neurological disorders. Lancet 363(9413):978–988
36. Repping-Wuts H, Fransen J, van Achterberg T, Bleijenberg G, van Riel P (2007) Persistent severe fatigue in patients with rheumatoid arthritis. J Clin Nurs 16(11C):377–383
37. Nijs J, Aerts A, De Meirleir K (2006) Generalized joint hypermobility is more common in chronic fatigue syndrome than in healthy control subjects. J Manip Physiol Ther 29(1):32–39
38. Verbraecken J, Declerck A, van de Heyning P, de Backer W, Wouters EF (2001) Evaluation for sleep apnea in patients with Ehlers-Danlos syndrome and Marfan: a questionnaire study. Clin Genet 60(5):360–365
39. Naughton F, Ashworth P, Skevington SM (2007) Does sleep quality predict pain-related disability in chronic pain patients? The mediating roles of depression and pain severity. Pain 127(3):243–252
40. Wessely S (1995) The epidemiology of chronic fatigue syndrome. Epidemiol Rev 17(1):139–151