Association of autonomic nervous system abnormalities on head-up tilt table test with joint hypermobility

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Abstract

Aim: The aim of this study was to investigate the association of autonomic nervous system abnormalities on head-up tilt table test (HUTT) with generalized joint hypermobility, expressed by Beighton score (BS).

Methods: This was a prospective study that included 115 consecutive patients (91 females, mean age 34.35±14.11) referred either for the HUTT or testing of the cardiovascular autonomic reflexes together with HUTT. Generalized joint hypermobility was evaluated according to the Beighton score (BS) system after which head-up tilt table test (HUTT) was performed. Clinically significant BS was considered if ≥4.

Results: Fifteen patients (15.1%) had BS ≥4. Results of the HUTT were normal in 58 (50.4%) patients and in 57 (49.6%) patient HUTT was abnormal. Fifteen (13.0%) patients fulfilled criteria for OH, 30 (26.1%) for reflex syncope and 21 (18.3%) for POTS. Patients with pathological findings on HUTT had significantly higher BS compared to patients with normal HUTT (median 1 vs. 0, p=0.001). There was a significant association between participants with BS ≥4 and pathological HUTT ($\chi(1)=6.392$, p=0.011). Results of the multivariate regression analysis revealed that increase in the Beighton score is associated with the increased likelihood of HUTT pathology (Exp(B) 1.44, 95%CI 1.084 – 1.922, p=0.012), while increase in age is associate with lower risk of HUTT pathology (Exp(B) 0.968, 95%CI 0.939 – 0.998, p=0.036).

Conclusion: There is an association between autonomic nervous system abnormalities on HUTT test and generalized joint hypermobility.

Key words: joint hypermobility, tilt table test, Beighton score.

Introduction

Joint hypermobility is relatively common, occurring in about 2-57% of different populations [1,2]. One of the most commonly used tests for the diagnosis of joint hypermobility is Beighton scoring (BS) and a cut-point of 4 is considered clinically significant [3,4]. There are many factors influencing the BS, like age, gender, ethnicity, and physical fitness [5]. Age is one of important factors influencing joint hypermobility. While the prevalence of joint hypermobility in girls from the UK, with the average age of 13.8 years, was 27.5% in one study, only 0.1% of the aging female population in UK had joint hypermobility using the same criteria in another study [6,7].

Although asymptomatic in majority of affected individuals, joint hypermobility has been associated with orthostatic intolerance syndromes, most commonly postural orthostatic tachycardia syndrome (POTS) [8]. However, studies further assessing this relationship are lacking. On the other hand, it has been shown that patients with joint hypermobility/Ehlers-Danlos syndrome (EDS-HT) are commonly burdened with orthostatic symptoms [8]. As well, EDS-HT patients frequently experience orthostatic intolerance [9]. It is still unclear whether there is an association between joint hypermobility features and orthostatic response in population without EDS-HT referred to autonomic nervous system testing. Therefore, the aim of this study was to investigate the association of autonomic nervous system abnormalities on head-up tilt table test (HUTT) with generalized joint hypermobility, expressed by BS.

Materials and methods

Patients

This was a prospective study that included consecutive patients referred to the Laboratory for Autonomic Nervous System Testing in the Department of Neurology, University Hospital Center Zagreb, Croatia, a referral center for autonomic nervous system disorders, either for the head-up tilt table test (HUTT) or testing of the cardiovascular autonomic reflexes together with HUTT. The study was performed from

January 2017 till April 2017. Patients with systemic rheumatic disease and cardiac disease were not included in the study. None of the patients were previously diagnosed with Ehlers-Danlos syndrome. Ethical committee of the University Hospital Center Zagreb approved the study. All participants signed informed consent.

Generalized joint hypermobility

Generalized joint hypermobility was evaluated according to the BS system [3]. The evaluation was performed by a single neurologist (IA) in all patients, before all other study procedures and the evaluator was blinded for the patients' diagnoses.

A score of 1 was given for each test the patient was able to perform including the following: (1) passive dorsiflexion of the little fingers beyond 90º, (2) passive apposition of the thumbs to the flexor aspects of the forearms, (3) hyperextension of the elbows beyond 10º, (4) hyperextension of the knees beyond 10º and (5) forward flexion of the trunk with the palms of the hands resting easily on the floor with knees being straight.

Range of the score is from 0 to 9 and clinical significant BS was considered if ≥4 [3].

Autonomic nervous system testing

The HUTT was performed according to the previously published protocol and performed on the Task Force Monitor (TFM), CNSystems Medizintechnik AG, Austria [10].

Results of HUTT were interpreted as orthostatic hypotension (OH), postural orthostatic tachycardia syndrome (POTS) or reflex syncope:

1) OH was defined as a sustained drop of systolic ≥20 mm Hg or diastolic blood pressure ≥10 mm Hg within 3 min of head-up tilt to 70° on a tilt table [11].
2) POTS was defined as the presence of symptoms of orthostatic intolerance associated with the increment of heart rate (HR) ≥30 bpm for adults, and ≥40 bpm for patients younger than 19 years on passive tilt and in the absence of orthostatic hypotension [11].

3) Reflex syncope was diagnosed and classified according to the modified VASIS classification [12].

Statistical analysis

Statistical analysis was performed using the IBM SPSS software, version 20. Differences in the distribution of qualitative variables were determined with the χ^2 test, while the differences in quantitative variables were determined with the use of nonparametric Mann–Whitney test. To determine the correlation between the variables, the Spearman correlation method was used. Multivariate logistic regression was used in order to determine which variables are significant predictors for specific model. P values less than 0.05 were considered as significant.

Results

During the study period 115 patients met the inclusion criteria (91 females, mean age 34.35±14.11). Referral diagnoses were: transient loss of consciousness (TLOC) due to presumed reflex syncope in 72 (62.6%), TLOC due to presumed seizure in 9 (7.8%), orthostatic intolerance in 18 (15.7%), dizziness in 8 (7.0%), multiple sclerosis in 2 (1.7%), limb paresthesiae in 1 (0.9%), diabetes in 2 (1.7%), vertigo in 1 (0.9%), and recurrent falls in 2 (1.7%) patients.

Beighton score (BS) was 0 in 65 (56.5%) and ≥1 in 50 (43.5%) patients (BS was 1 in 12 (10.4%), 2 in 19 (16.5%), 3 in 4 (3.5%), 4 in 6 (5.2%), 5 in 5 (4.3%) patients, while values of BS 6, 7, 8 and 9 were present in 1 (0.9%) patient for each value). There was no statistically significant difference between male and female in the Beighton score (p=0.079), but there was statistically significant correlation between the Beighton score and age (r_s=-0.293, p=0.001). Out of the patients with BS ≥4, referral diagnoses were TLOC due to presumed reflex syncope in 8 (53.3%), orthostatic intolerance in 3 (20%), TLOC due to presumed seizure in 1 (6.7%), dizziness in 1 (6.7%), multiple sclerosis in 1 (6.7%), and limb paresthesiae in 1 (6.7%) patient.

Results of the HUTT were normal in 58 (50.4%) patients and in 57 (49.6%) patient HUTT was abnormal. Fifteen (13.0%) patients fulfilled criteria for OH, 30 (26.1%) for reflex syncope and 21 (18.3%) for POTS. Demographic data depending on the result of the HUTT are presented in Table 1. Patients with POTS and reflex syncope were statistically significant younger (27.3±12.3 vs. 38.4±13, p=0.001; and 28.6±13.1 vs. 38.4±13, p=0.001; respectively), while there was no statistically significant difference between patients with OH and patients with no pathology (p=0.919).

Patients with pathological findings on HUTT had significantly higher BS compared to patients with normal HUTT (median 1 vs. 0, p=0.001). The same finding was observed for patients with OH, POTS and reflex syncope (all data are presented in Table 2). We found significant association between participants with BS ≥4 and pathological HUTT ($\chi(1)=6.392$, p=0.011) and also separately for each type of pathology (p=0.012 for OH, p=0.015 for POTS and p=0.030 for reflex syncope).

A multivariate logistic regression was performed in order to examine the influence of the gender, age and the Beighton score on the likelihood that patients have HUTT pathology. The logistic model was statistically significant, $\chi^2(3) = 18.009$, p<0.001 and it correctly classified 71.3% of cases. Results of the multivariate regression analysis revealed that increase in the Beighton score is associated with the increased likelihood of HUTT pathology (Exp(B) 1.44, 95%CI 1.084 – 1.922, p=0.012), while increase in age is associate with lower risk of HUTT pathology (Exp(B) 0.968, 95%CI 0.939 – 0.998, p=0.036).

Additionally, we performed a multivariate logistic regression on two separate models, one to examine the influence of Beighton score, sex and age on the likelihood that patients have POTS or reflex syncope and a second one to examine the influence of before mentioned predictors on the likelihood that patients have OH. Results are presented in Table 3.

Discussion

Results of this study demonstrate an association between autonomic nervous system abnormalities on HUTT and joint hypermobility. Patients with pathological findings on

HUTT had significantly higher BS compared to patients with normal HUTT. As well, there was a significant association of BS≥4 and pathological HUTT.

There are several previously published studies investigating possible association of different autonomic disorders with joint hypermobility. Patients with EDS-HT frequently experience orthostatic intolerance with a recent study showing that half of them have POTS [9]. It has been suggested that many of the non-musculoskeletal complaints in patients with EDS-HT have been attributed to an underlying dysautonomia [13,14].

There are several hypotheses on mechanism of dysautonomia in EDS-HT including peripheral neuropathy, connective tissue abnormalities and deconditioning. Studies using quantitative sudomotor axon reflex test (QSART) have shown evidence of small fiber neuropathy (peripheral sympathetic nerve dysfunction) [15]. In the same study, skin extensibility was identified as the most important predictor for the severity of sympathetic dysfunction [15], suggesting that the loss of connective tissue stiffness may lead to increased blood vessel distensibility resulting in more venous pooling during the upright position. The results of our multivariate regression analysis showing that the increase in the BS is associated with the increased likelihood of HUTT pathology, further supports this theory.

Results of the present study have also shown a significant number of BS positive patients with OH, as well as POTS. Although the association of both POTS and OH with the same pathological background might sound counterintuitive, given that OH essentially excludes POTS when present in the same patient, this is not necessarily contradictory when we examine the patophysiological mechanisms of these conditions. Namely, OH is a result of inadequate return of blood from the lower extremities and splanchnic circulation due to impaired vasoconstriction [16]. Although the exact mechanisms that lead to POTS are not entirely known it is established that excessive blood pooling in the legs while standing due to increased venous capacitance contributes to the occurrence of this disorder [17]. Another proposed mechanism is increased blood flow in the legs caused by microvascular filtration that leads to compensatory tachycardia, albeit without a drop in blood pressure [18]. Therefore, increased retention of blood in the lower extremities upon passive tilting

due to increased blood vessel elasticity and venous stasis can lead to POTS or OH depending on the extent and type of the connective tissue pathology. As well, the same mechanism predisposes to reflex syncope which has been demonstrated in a study using negative lower body pressure during HUTT [19].

Finally, one study has shown that position sense at the proximal interphalangeal joint was found to be significantly impaired in patients with joint hypermobility [24], suggesting that neurological abnormalities might play a role as well. This finding is interesting in the light of the association of OH, a structural disorder of the autonomic nervous system, and the BS in the present study. It can be hypothesized that if neurological disorders, which often have dysautonomia, influence proprioception, joint hypermobility might develop as well.

This study has several limitations. There is no healthy control group where the hypermobility trait is tested or a comparative population of patients with pure joint hypermobility alone with the tests for autonomic function, however the main objective of our study was to to investigate the association of autonomic nervous system abnormalities on head-up tilt table test (HUTT) with generalized joint hypermobility in population of patients referred for autonomic nervous system testing. Furthermore, we have not systematically collected data regarding symptoms of joint hypermobility nor the presence of vascular features suggestive of EDS-HT.

Nevertheless, the significance of this study results are twofold. Firstly, patients with disorders of orthostatic tolerance should be screened for joint hypermobility as this might explain their predisposition to these disorders and if present should be warned about potential joint dislocation that persons with joint hypermobility are usually prone to. Secondly, patients with joint hypermobility should be specifically questioned for orthostatic symptoms as, according to the presented results, it may predispose them to orthostatic intolerance.

In conclusion, results of current study demonstrate that there is an association between joint hypermobility and pathological response to orthostatic provocation, warranting further research of this association.

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Tables

	Age (mean+/-SD)	Beighton score (median, range)	Female (%)
No pathology	38.4+/-13	0 (0-5)	79%
OH	38.0+/-17.2	2 (0-8)	93%
Reflx syncope	28.6+/-13.1	1 (0-9)	67%
POTS	27.3+/-12.3	1 (0-5)	81%

Table 1. Demographic data depending on the result of the head-up tilt table test (HUTT). SD - standard deviation, OH – orthostatic hypotension, POTS – postural orthostatic tachycardia syndrome

		BS 0	BS ≥4	p
HUTT pathology	No	55	3	0.011
	Yes	45	12	
OH	No	55	3	0.012
	Yes	11	4	
POTS	No	55	3	0.015
	Yes	16	5	
Reflex syncope	No	55	3	0.030
	Yes	24	6	

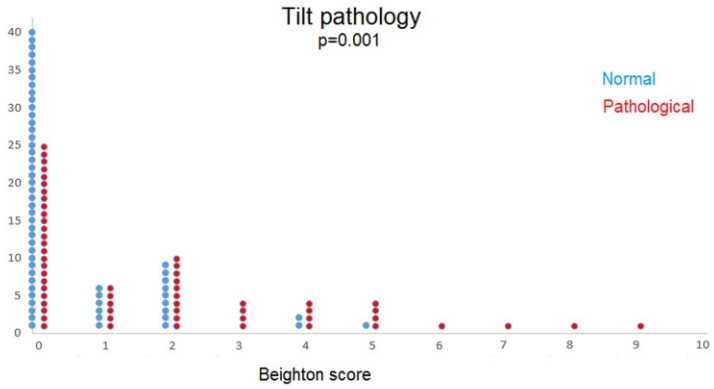
Table 2. Association between participants with BS ≥4 and HUTT pathology. BS - Beighton score. HUTT - head-up tilt table test, OH - orthostatic hypotension, POTS - postural orthostatic tachycardia syndrome.

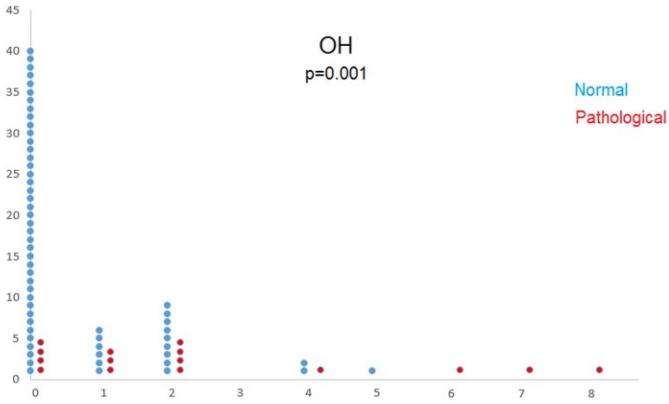
	Exp(B)	95% C.I. for EXP(B)		p value
POTS or reflex syncope				
Beighton score	1.390	1.014	1.903	0.040*
Sex	0.617	0.222	1.716	0.355
Age	0.946	0.912	0.982	0.004*
OH				
Beighton score	1.790	1.208	2.652	0.004*
Sex	2.084	0.232	18.716	0.512
Age	1.028	0.979	1.078	0.268

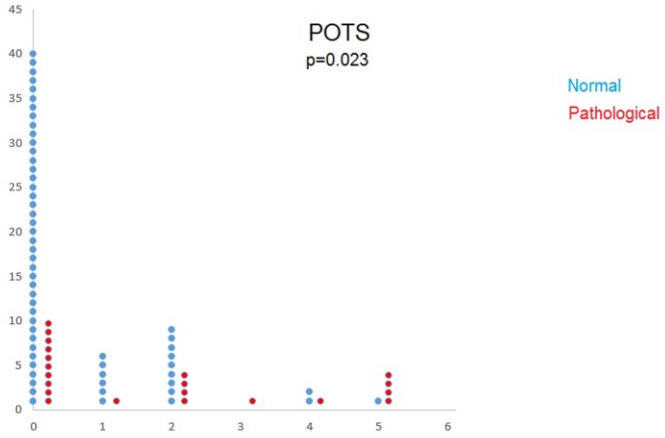
Table 3. Results of the two multivariate logistic regression models showing that the Beighton score and age are statistically significant predictors for POTS or reflex syncope, but only the Beighton score is statistically significant predictor for OH.
C.I. – confidence interval, OH - orthostatic hypotension, POTS - postural orthostatic tachycardia syndrome.

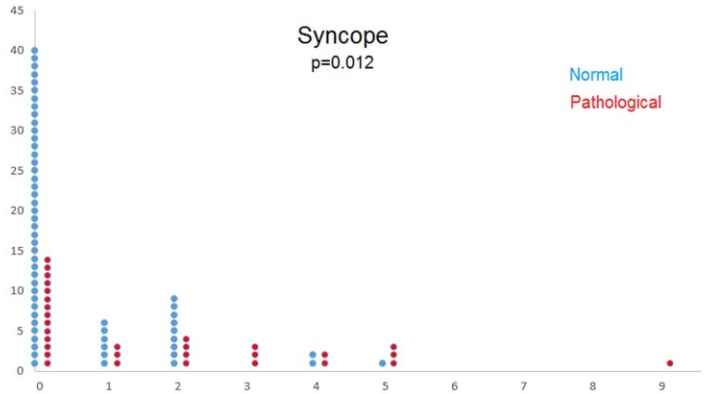
Figures

Figure 1. Difference in the Beighton score regarding the HUTT pathology. HUTT - head-up tilt table test. BS - Beighton score. OH - orthostatic hypotension. POTS - postural orthostatic tachycardia syndrome.


Tilt pathology
p=0.001
Normal
Pathological
Beighton score


OH
p=0.001
Normal
Pathological


POTS
p=0.023
Normal
Pathological


Syncope
p=0.012
Normal
Pathological