A new insight on postural tachycardia syndrome in 102 adults with hypermobile Ehlers-Danlos Syndrome/hypermobility spectrum disorder

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Abstract

There is an association between joint hypermobility, hypermobile Ehlers-Danlos syndrome (hEDS) and different forms of orthostatic intolerance. Objective: to explore autonomic profile in a large cohort of adults with hEDS and hypermobility spectrum disorder (hEDS/HSD) with a multimodal approach. In this observational retrospective study, heart rate, blood pressure and baroreflex sensitivity were estimated in 102 hEDS/HSD subjects during deep breathing, Valsalva maneuver, standing up: 30-15 ratio, Head-Up Tilt and sustained handgrip. Abnormal results and head-up tilt test were common and included postural orthostatic tachycardia syndrome (POTS; 48%), orthostatic intolerance (25.5%) and hypotension (3.9%). Baroreflex sensitivity was significantly different in individuals with POTS compared to the others. This study confirms the high rate and heterogeneity of abnormal autonomic regulation in hEDS/HSD, and suggests the baroreflex sensitivity might distinguish comorbid POTS from other profiles in this subgroup of patients. Abnormal autonomic regulation is common in adults with hEDS/HSD and should be regularly assessed for tailoring the management approach.

Introduction

There is a strong association between joint hypermobility, hypermobile Ehlers-Danlos syndrome (hEDS) and different forms of orthostatic intolerance, mostly postural orthostatic tachycardia syndrome [1]. In particular, in the last decade, increasing evidence indicates that a significant proportion of individuals with joint hypermobility syndrome (JHS), which has been dismissed by the current nosology and is now, included within the hypermobility spectrum disorders (HSD) [2], and hEDS present with fatigue and a series of dysautonomic symptoms which significantly affect quality of life of these patients [3]. Treatment measures for these manifestations in this patients’ category is currently the same of the general population, but their management remains often unsatisfactorily in the real-world medicine due to the lack of shared recommendations aimed at exploring the heterogeneous pathogenesis of these symptoms in the clinical practice. Accordingly, we previously demonstrated abnormal cardiovascular autonomic profiles and, in particular, a higher baroreflex sensitivity (BRS) in 35 adults with hEDS and JHS [4]. Other research groups in cohorts of adults and children with similar sample sizes [4-8] have obtained overlapping results. Nevertheless, little is known about the clinical applications of this evidence in hEDS/HSD.

The aim of this study was to explore patterns of autonomic regulation in a bigger patients’ cohort with hEDS/HSD and to identify possible distinguishing features among the various cardiovascular autonomic patterns in such a heterogeneous phenotypic spectrum.

Patients and Methods

Population

Enrolled patients were originally assessed according to Brighton and Villefranche criteria [9,10]. The distinction between...
these two sets of criteria was subsequently attenuated with the
introduction of a single phenotypic class termed JHS/hEDS [11].
The new international classification presents stricter criteria for
hEDS and introduces a broader phenotype HSD to include all
symptomatic patients who do not respect the new hEDS criteria
[2]. Accordingly, our patients’ sample was redefined as
hEDS/HSD. Patients recruited have all symptoms related to
orthostatic intolerance.

Examination
Following preliminary evidence, all patients underwent
assessment by an autonomic cardiovascular lab - syncpe unit as
part of the routine multispecialty evaluation for adults HSD/hEDS.
ECG and blood pressure signals were noninvasively acquired by
using the Task Force Monitor (CNSytem). Heart rate variation,
blood pressure response and baroreflex sensitivity (BRS) were
estimated by the device software. Tests included Cardiovascular
ReFlex Tests (deep breathing, Valsalva maneuver, standing up: 30-
15 ratio, blood pressure response to sustained handgrip), and
Head-Up Tilt test.

An expert consensus statement defines Postural Orthostatic
Tachycardia Syndrome (POTS), a form of chronic orthostatic
intolerance, as a heart rate increment ≥30 beats/min within 10 min
of standing or head-up-tilt (HUT) which is sustained in the
absence of orthostatic hypotension (a drop ≥20 mmHg in systolic
blood pressure or >10 mmHg in diastolic body pressure) [6].

Deep breathing
Participants breathed maximally at a frequency of 6 breaths
per minute, following the lead of an oscillating ball on a computer
screen. The deep breathing test was considered normal if heart rate
(HR) variation was 15 beats/min or more, borderline if 11-14
beats/min, and pathological if 10 beats/min or less. The HR range
was calculated as a measure of parasympathetic reactivity [6].

Valsalva maneuver
Individuals blew into a mouthpiece between 40 and 50 mmHg
for 15 s. The Valsalva ratio (VR) was calculated, and the 4 phases
of blood pressure (BP) response were quantified [13]. Respect to
the baseline, the maximal drop of systolic and diastolic BP (SBP
and DBP) at the different phases during Valsalva maneuver were
computed.

Standing up
Subjects were asked to stand at rest in the supine position for
5 min and, then, to assume the standing position without help as
quickly as possible according to his/her physical abilities. The
cardiac chronotropic response characteristic is expressed by the
ratio 30:15; this ratio means the longest R-R interval after the
maneuver (around the thirtieth beat) and the shortest R-R interval
≤1.00 [4].

Sustained handgrip
Handgrip was maintained at 30% of maximal voluntary
contraction until the maximum time of 5 min by using a
dynamometer. Handgrip test was considered successfully
performed if patients were able to maintain a constant effort for
at least 1 min.

Head-up tilt
The participant firstly rested in supine position quietly for 5
min. Baseline HR and BP were calculated as the mean from 40 s
to 10 s before tilting. Next, the table was tilted upright to an angle
of 70° for a maximum of 20 min. Orthostatic hypotension (OH)
was defined as a sustained diastolic BP drop of at least 10 mmHg
or a systolic BP drop of at least 20 mmHg [13]. Postural orthostatic
tachycardia (POTS) was defined as a sustained HR rise of at least
30 bpm or a HR of at least 120 bpm in the first 10 min of tilt,
without concomitant orthostatic hypotension [14].

BRS was assessed using the sequence method in which “up”
and “down” sequences are identified (CNSystems Task-Force
Monitor 3040i). Up sequences consist of four or more consecutive
cardiac cycles for which there is a sequential rise in both systolic
pressure and R-R interval. Down sequences consist of four or
more cardiac cycles for which there is a sequential fall in systolic
pressure and R-R interval. Values of cardiac BRS were accepted
when the number of sequences was ≥3 for both up and down
sequences [14,15].

Statistical analysis
Student’s paired t-test was used to compare differences in the
spectral variables between rest and tilt. Student’s unpaired t-test
was used to compare differences in the spectral variables between
groups. A p-value of <0.01 was considered to indicate statistical
significance.

Results
A total of 102 hEDS/HSD individuals (90 females and 12
males, mean age 34±13) were evaluated. Among the group about
48% of the patients referred syncopeal and pre-syncopeal
symptoms, 18.6% complained fatigue, 16.6% tachycardia, 8.8%
vertigo and 7.8% cephalalgia. Table 1 shows that DB test, 30/15
ratio and VR gave normal results in most patients. All subjects
failed to complete the sustained handgrip test due to pain and
fatigue. Seventy-five individuals (73.5%) were able to perform
the Valsalva maneuver, while the remaining (27.5%) were not
due to breathing difficulties and incoordination. In those who
completed the Valsalva maneuver, we observed both the increase
of blood pressure (BP) between early and late phase II, and the
overshoot in late phase IV, according to the normal values
(Table 2).

Ninety-nine out of 102 subjects completed the HUT test.
Among them, 49 (49.49%) showed POTS, 26 (26.26%)
orthostatic intolerance and 4 (4.04%) orthostatic hypotension,
while the remaining (20.20%) showed a normal response.
Percentages about heart rate (HR) and BP for each categories are
comparable to the previous study with a net predominance of
POTS (48%) and orthostatic intolerance (25.5%) in the patients’
sample (Table 3).

The BRS values were estimated and compared at rest and
during the HUT test in the two POTS hEDS/HSD (individuals
with POTS at HUT test) versus non-POTS-hEDS/HSD (individuals
without POTS at HUT test) and POTS hEDS/HSD versus Normal
subjects (Table 4). Subjects with orthostatic hypotension at HUT
were excluded from this analysis.

At rest, POTS hEDS/HSD subjects showed higher BRS values
compared to non-POTS hEDS/HSD (p<0.03) and normal-
hEDS/HSD (p=0.009) subjects.
Table 1. Response to cardiovascular reflex tests.

<table>
<thead>
<tr>
<th>Test (Total #102)</th>
<th>Normal number (%)</th>
<th>Borderline number (%)</th>
<th>Pathological number (%)</th>
<th>Not evaluable number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep breathing</td>
<td>100 (98)</td>
<td>-</td>
<td>-</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>70 (68.6)</td>
<td>5 (4.9)</td>
<td>-</td>
<td>27 (26.4)</td>
</tr>
<tr>
<td>30/15 ratio</td>
<td>80 (78.4)</td>
<td>20 (19.6)</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Sustained handgrip</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>102 (100)</td>
</tr>
</tbody>
</table>

Table 2. Results of Valsalva maneuver in the 75 hEDS/HSD individuals.

<table>
<thead>
<tr>
<th>Variable</th>
<th>mmHg ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SBP/DBP</td>
<td>111.5 ± 10.9</td>
</tr>
<tr>
<td>Maximal drop of SBP during early phase II</td>
<td>71.6 ± 8.1</td>
</tr>
<tr>
<td>Maximal drop of DBP during early phase II</td>
<td>10.7 ± 14.6</td>
</tr>
<tr>
<td>SBP at late phase II</td>
<td>114.3 ± 18.3</td>
</tr>
<tr>
<td>DBP at late phase II</td>
<td>81.1 ± 14.5</td>
</tr>
<tr>
<td>SBP at late phase IV</td>
<td>126.3 ± 20.2</td>
</tr>
<tr>
<td>DBP at late phase IV</td>
<td>79 ± 13.7</td>
</tr>
<tr>
<td>Difference between late phase II SBP and early phase II SBP</td>
<td>24.7 ± 13.6</td>
</tr>
<tr>
<td>Difference between late phase II DBP and early phase II DBP</td>
<td>14.7 ± 9.5</td>
</tr>
</tbody>
</table>

Normal values: Maximal drop of mean blood pressure (MBP) during early phase II: ≥20 mmHg; systolic blood pressure (SBP) and diastolic blood pressure (DBP) at late phase II: ≥baseline; SBP and DBP at late phase IV: ≥baseline.

Table 3. Heart rate (HR) and blood pressure responses after head-up tilt test.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>HR response ratio (%)</th>
<th>HR mean difference (bpm ± SD)</th>
<th>BP response ratio (%)</th>
<th>SBP mean difference (mmHg ± SD)</th>
<th>DBP mean difference (mmHg ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>20 (19.6)</td>
<td>12.5 ± 4.3</td>
<td>Normal</td>
<td>96 (94.1)</td>
<td>6.5 ± 6.1</td>
</tr>
<tr>
<td>POTS/HR increase &gt;30 bpm</td>
<td>49 (48)</td>
<td>37 ± 6.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced orthostatism tolerance</td>
<td>26 (25.5)</td>
<td>23.5 ± 3</td>
<td>Orthostatic hypotension (reduced peripheral vessel response)</td>
<td>3 (2.9)</td>
<td>-2.5 ± 21</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>4 (3.9)</td>
<td>28 ± 2.6</td>
<td></td>
<td></td>
<td>-16.2 ± 2.5</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3 (2.9)</td>
<td>-</td>
<td>Not evaluable</td>
<td>3 (2.9)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4. Comparison of baroreflex sensitivity between hEDS/EDS individuals with and without POTS and between hEDS/EDS individuals with normal results at head-up tilt test.

<table>
<thead>
<tr>
<th>Test (mean ± DS ms/mmHg)</th>
<th>POTS-hEDS/HSD (49)</th>
<th>vs POTS-hEDS/HSD (50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest (mean ± DS ms/mmHg)</td>
<td>P (rest versus HUT)</td>
<td>21.4 ± 10.3*</td>
</tr>
<tr>
<td>HUT (mean ± DS ms/mmHg)</td>
<td>9 ± 3.6</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Normal-hEDS/HSD (20)</td>
<td>P (rest versus HUT)</td>
<td>21.4 ± 10.3**</td>
</tr>
</tbody>
</table>

*p < 0.05 POTS vs non-POTS; **p < 0.001 POTS vs normal.
Discussion

These findings confirm, in the largest patients’ cohort published to date, that ~50% of adults with hEDS/HSD present comorbid POTS and that a higher proportion of them shows an abnormal response at HUT test. As POTS and hEDS/HSD individuals share many chronic symptoms that might be ameliorated by treating the former, our study suggests testing hEDS/HSD individuals for POTS in a clinical setting for approaching a more tailored management program. Accordingly, a list of useful treatment resources for fatigue and cardiovascular dysautonomia have been recently reviewed for Ehlers-Danlos syndrome and related disorders [16,17].

Our study also proposes that, among adults with hEDS/HSD, those with POTS might be distinguished from the others by BRS estimated with sequences method during HUT. Therefore, we speculate that BRS indirect estimation in basal conditions could be considered an alternative for separating hEDS/HSD individuals with comorbid POTS from the others in the absence of accessibility to HUT test. If confirmed by further studies and/or in other populations, HUT test and BRS indirect estimation might be included, in combination or isolation, in future management guidelines for optimal treatment of cardiovascular dysautonomic manifestations in hEDS/HSD patients/adults, in association to management and rehabilitation strategy related to muscle hypotonia [18,19] in order to improve balance, stability and reduce cardiovascular dysautonomia.

There are some limitation in this study: firstly this is a retrospective evaluation and in a future a more organized study should be desirable; moreover a correlation between different symptoms and their intensity and, duration of the disease and possible other pathology or therapy should be useful.

Conclusions

In conclusion, this study present cardiovascular autonomic data in the largest patients’ cohort with HSD/hEDS published to date. We confirmed the high frequency of POTS and orthostatic intolerance in HSD/hEDS and their potential relevance in the clinical assessment of these patients. The existence of different autonomic profiles in our sample suggests discrete phenotypes within the HSD/hEDS spectrum. Further exploration of such heterogeneity may help in the identification of biomarkers useful for both clinical and molecular research.

References