EXTRA-ARTICULAR FEATURES OF BENIGN JOINT HYPERMOBILITY SYNDROME


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SUMMARY

To define the phenotype of patients with benign joint hypermobility syndrome (BJHS), we studied 58 consecutive patients (mean age 37 yr) presenting to a rheumatology clinic and 30 controls. Patients underwent rheumatological and ophthalmic examination, echocardiography, measurement of bone mineral density (BMD), and skin thickness, elasticity and light transmissibility. The median hypermobility score was 5/9 Beighton and 31/56 Contompasis. Eighteen (31%) patients complained of significant arthralgia. Six (10%) patients and two (7%) controls had mitral valve prolapse (MVP) ($\chi^2 = 0.27, P = NS$). Neither MVP nor aortic diameters showed a correlation with hypermobility score. There was no significant reduction in BMD. There was a significant correlation between hypermobility and light transmissibility of the skin ($r = 0.71, P < 0.0001$ Contompasis; $r = 0.47, P < 0.05$ Beighton) and skin stretchiness ($r = 0.49, P < 0.05$ Contompasis; $r = 0.39, P < 0.05$ Beighton). On ophthalmic examination, 14 (41%) patients had upper eyelid laxity. Thus, patients with BJHS do not have an increased prevalence of significant cardiac, bone, skin or eye abnormalities, helping differentiate BJHS from other more serious hereditary disorders of connective tissue.

KEY WORDS: Joint hypermobility, Echocardiography, Skin measurements, Ophthalmic examination, Bone density.

The benign joint hypermobility syndrome (BJHS) is a common benign hereditary overlap disorder of connective tissue (HDCT), which incorporates many of the classical features seen in the major HDCTs such as the Marfan (MFS) and Ehlers–Danlos (EDS) syndromes, and osteogenesis imperfecta. Patients with BJHS usually present with arthralgia, traumatic or overuse soft tissue lesions, recurrent joint dislocation or subluxation, or low-grade inflammatory or degenerative arthritis. BJHS has been defined as the occurrence of musculoskeletal symptoms in hypermobile subjects in the absence of systemic rheumatological disease [1].

Since BJHS was first described [1], there has been much interest in further characterizing the clinical features and establishing its genetic basis. There have also been concerns about the benign nature of the disorder with some studies showing an increased incidence of cardiological problems, such as mitral valve prolapse (MVP), in patients with BJHS [2–4].

Cardiovascular abnormalities are found in the HDCTs and may play a major role in prognosis. For instance, 85% of deaths in MFS are thought to be due to cardiac causes [5]. The pathogenesis of these complications is thought to be through defects of collagen or the microfibrillary system. Cardiac findings in the HDCTs may range from minor MVP to life-threatening aortic dilatation and dissection. Skin and bone abnormalities have been clearly defined in these syndromes. However, the incidence of abnormalities in the cardiovascular system, skin and bone in BJHS is unclear.

Previous studies have given conflicting results, with an incidence of MVP from 8 to 60% [3, 4, 6]. There has been no previous systematic study of skin, bone and cardiovascular findings in patients with BJHS.

The purpose of the current study was to define the BJHS phenotype using a multidisciplinary approach in order to distinguish it diagnostically from the eponymous HDCTs and as a prelude to molecular genetic studies.

PATIENTS AND METHODS

We examined 58 consecutive patients (52 female, six male; 56 Caucasian, one Afro-Caribbean, one Asian) with BJHS attending the rheumatology clinic at Guy’s Hospital. Their mean age was 37 yr (range 15–79). Approval for the study was given by the Guy’s Hospital Ethics Committee.

Musculoskeletal and skin examination

Joint hypermobility was measured using the Beighton [7] and Contompasis [8] scales. BJHS was diagnosed using the draft criteria shown in Fig. 1 [9, 10]. Beighton scores of >3 (Contompasis score >20) reflect generalized joint hypermobility. Skin stretchiness was estimated by lifting a skin fold on the dorsum of the hand and graded from 0 (normal) to 3 (very stretchy). The presence of papyraceous scars or striae was noted. Skin thickness and light transmissibility were measured on the dorsum of the hand using the modified Harpenden calliper [11], and the modulus of elasticity was determined using the suction cup method on the dorsal forearm [12].

Cardiac assessment

Cardiac assessment included standard 12-lead electrocardiography (ECG) and echocardiography.

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using the Vingmed CFM 750 system with a 3.5 MHz Duplex probe. Mitral valve prolapse was defined as either (i) movement of the point of closure (coaptation point) of the mitral leaflets behind the plane of the mitral annulus into the left atrium during systole assessed in the apical four chamber view or (ii) movement of a part of either leaflet above the plane of the annulus into the left atrium during systole assessed in the parasternal long axis view.

Aortic dimensions were assessed on frozen two-dimensional views taken parasternally for the aortic root, from the suprasternal notch for the aortic arch and 5 cm below the xiphisternum for the abdominal aorta.

Thirty age- and sex-matched controls from the normal population (27 female, three male) were also studied as part of the cardiac assessment.

**Bone densitometry**

Forty subjects underwent bone density measurement on the Hologic QDR-1000 [13] with measurement of bone mineral density (BMD) at the lumbar spine (L1–L4), femoral neck and three sites in the distal forearm (ultradistal, mid-distal and distal 1/3 radius). Results were compared with those for age-matched normal subjects obtained from the Hologic database, previously validated against a population-based database [14], and Z scores obtained using the following formula:

\[
Z = \frac{\text{BMD} - \text{BMD (normal)}}{\text{S.D.}}
\]

**Ophthalmic assessment**

Thirty-four patients (mean age 38 yr; 32 female, two male) also underwent assessment by an ophthalmic surgeon for features known to occur in the HDCTs. Abnormalities of refraction, lids and external eye, anterior segment, lens and fundus were sought using pupillary dilatation and slit-lamp examination. Increased lid laxity was diagnosed if the lower lid could be pulled away from the globe by at least 10 mm and returned to the resting position more slowly than normal, and the upper lid could be pulled away from the globe more easily than normal and everted easily. The presence of redundant lid tissue was also noted and excess lid skin diagnosed if the skin fold overhanging the crease was greater than normal for the subject's age.

**Statistical analysis**

The \( \chi^2 \) test was used for categorical variables and correlation coefficients were calculated where appropriate. BMD was analysed using Z scores as described above.

**RESULTS**

**Diagnostic criteria**

The median Beighton hypermobility score was 5/9 (range 0, in a patient with previously documented hypermobility, to 9) and 31/56 on the Contompasis scale (range 23–50). Figure 2 shows Beighton score by age of patients. Younger patients (<35 yr) were more likely to have Beighton hypermobility scores of >6. Median hypermobility scores for the control group were 2/9 Beighton and 22/56 Contompasis.

Of the major criteria, 51 (88%) patients had a Beighton score of >4, while 40 (69%) had arthralgia for > 3 months in more than four joints. The most commonly identified minor criteria were Marfanoid habitus (in 35%), arthralgia in 1–3 joints (in 31%) and skin striae, hyperextensibility or scarring (in 27%). A history of varicose veins, hernia or visceral prolapse was elicited in 19% of patients with 10% having suffered soft tissue lesions such as ligament injury. Five subjects had a history of soft tissue lesions such as capsulitis, tendinitis and epicondylitis. A history of joint dislocation was very uncommon, occurring in only two (4%) of the study population.

**Fig. 1.—Draft diagnostic criteria for benign joint hypermobility syndrome. To fulfil the diagnostic requirements, patients must have two major or one major and two minor or four minor criteria in the absence of any systemic rheumatological disease. Major criterion 2 and minor criterion B are mutually exclusive.**
**Cardiovascular findings**

Two patients had murmurs on auscultation; both were short ejection systolic murmurs louder on expiration and were thought to be benign flow murmurs. Two patients had minor abnormalities on ECG (right axis deviation in a patient with a normal echo study, abnormal P wave axis in a patient with MVP).

Six patients (10%) had MVP on echocardiography (mean age 39 yr, all female), one with mild mitral regurgitation. There was no correlation between the hypermobility score measured by either scale and MVP (Fig. 3). In three patients, the Beighton score was <5 and in three it was >5. There was also no significant correlation between hypermobility, skin stretchiness, marfanoid habitus and the presence of MVP (Table I). Seven per cent of the control group had mild mitral valve prolapse on echocardiography. The difference between controls and the study population was not statistically significant ($x^2 = 0.27, P > 0.5$).

Mean aortic root diameter was 2.6 cm (range 2.1–3.0 cm, normal range 2–4 cm). Figure 4 shows mean aortic diameters corrected for body surface area for three groups of patients. There is no significant difference in diameter at each level between mild (score 0–3), moderate (score 4–6) or severely (score 7–9) hypermobile patients.

**Skin findings**

Median skin stretchiness was two with no significant correlation between skin stretchiness or light transmissibility and the presence of MVP. There was a highly significant correlation between light transmissibility and hypermobility score as measured using the Contompasis scale ($r = 0.706, P < 0.0001$), and a less strongly significant correlation using the Beighton score ($r = 0.467, P < 0.05$). There was also a correlation between skin stretchiness and hypermobility scores (Beighton score, $r = 0.393, P < 0.05$; Contompasis score, $r = 0.490, P < 0.05$).

Twenty-four patients (two male, 22 female; median Beighton score 5/9, median Contompasis score 33/56) also attended for measurement of skin stretchiness. There was no significant correlation between the mean modulus of elasticity and BMD, aortic diameter and Beighton score ($r = 0.005, P = NS$).

**Bone density**

Table II shows BMD Z scores at each site. BMD was marginally reduced in BJHS patients at the femoral neck and lumbar spine as compared to a normal population, with the difference being most marked in those <45 yr of age. However, these differences did not reach statistical significance. No significant correlation

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![FIG. 2.—This shows the number of patients in each age group with low (0–3), moderate (4–6) and high (7–9) Beighton hypermobility scores.](image)

![FIG. 3.—Patients with mitral valve prolapse are shown by Beighton hypermobility score.](image)

**Table I**

<table>
<thead>
<tr>
<th>Clinical characteristics of patients with mitral valve prolapse</th>
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<tbody>
<tr>
<td><strong>Patient</strong></td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>PW</td>
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<tr>
<td>JA</td>
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<tr>
<td>PP</td>
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<tr>
<td>KS</td>
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<td>MJ</td>
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either Beighton (r = 0.04, P = NS) or Contompasis (r = 0.12, P = NS) hypermobility scores.

Ophthalmic findings
Corrected visual acuity was normal in all but two patients who were known to have unilateral amblyopia. Ocular motility was normal in all but one patient with a long-standing divergent squint. There was a small excess of myopia, with four patients having a refractive error of > 3.00 dioptres (D). However, 88% of patients had errors between −3 D and +3 D. The eyelids were judged to be abnormal in 23 (68%) patients. The most common abnormality, seen in 14 (41%) patients, was excess lid laxity. An additional eight patients (24%) had prominent horizontal folds of upper lid skin. One patient had congenital unilateral ptosis. No significant abnormalities of sclera, cornea or iris were found on slit-lamp examination. All lenses were stable with no subluxation. The only fundal abnormality was in three patients with tilted optic discs. No angioid streaks were seen.

TABLE II
Bone density at each locus shown as Z scores (see the text for formula) with t-test results. Results are also shown for those aged <45 yr

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of patients</th>
<th>Mean Z score</th>
<th>t value</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>40</td>
<td>−0.216</td>
<td>1.11</td>
<td>NS</td>
</tr>
<tr>
<td>Femur</td>
<td>40</td>
<td>−0.304</td>
<td>1.73</td>
<td>NS</td>
</tr>
<tr>
<td>Distal forearm</td>
<td>30</td>
<td>0.008</td>
<td>0.0004</td>
<td>NS</td>
</tr>
<tr>
<td>Under 45 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>26</td>
<td>−0.297</td>
<td>1.37</td>
<td>NS</td>
</tr>
<tr>
<td>Femur</td>
<td>26</td>
<td>−0.401</td>
<td>2.03</td>
<td>NS</td>
</tr>
</tbody>
</table>

DISCUSSION
Cardiac abnormalities are an important part of the HDCTs and have been described in MFS [15–17], EDS [18–20] and osteogenesis imperfecta [21]. Previous studies have also suggested that cardiac abnormalities are a common finding in BJHS, but have given conflicting estimates of their incidence.

In the 1980s, Jessee et al. [6] found that two of 23 (8%) healthy blood donors with joint hypermobility had MVP, while Grahame et al. [22] in a study using M-mode echocardiographic definition of MVP found an incidence of 33% in 51 patients with BJHS as compared to two of 25 controls (8%). In another study from the same centre, Handler et al. [4] used both two-dimensional and M-mode echo to identify MVP, and found it in nine of 15 patients with BJHS (60%). This group was selected for a combination of high Beighton scores (>4) and signs of generalized connective tissue disorder. No aortic root or arch abnormalities have been reported in BJHS patients; however, there has been no systematic study of aortic dimensions in this group. It is logical to look for aortic dilatation in patients with BJHS given the known importance of such problems in the other hypermobility syndromes, in particular MFS.

We have not found an increased incidence of MVP in patients with BJHS (10% in the patient group vs 7% in the small control group). In the patient population, there was no significant correlation between the degree of hypermobility and the presence of MVP, with three patients with MVP in the group with Beighton scores <5 and three in those with scores >5. In particular, it is noteworthy that in only one patient with MVP was it of a sufficient degree to result in mitral regurgitation. In all the other patients, there was minimal MVP only. The marked disparity in incidence of MVP between the studies is partly due to stricter criteria accepted for its definition [23–26], in particular the use of M-mode echocardiography in early studies without two-dimensional confirmation tends to overdiagnose MVP by inadvertent scanning of the base of the leaflets. The prevalence of MVP in the general population is 5–10% [27–29].

Aortic dimensions were also within normal limits in our patient population, thus helping to differentiate BJHS patients from those with MFS and confirming the benign nature of BJHS.

There has been no previous systematic study of skin, bone and eye findings in BJHS patients, although such abnormalities form part of the classical characteristics of the HDCTs. The only significant finding on ophthalmic examination was a high incidence of lid laxity or redundant lid tissue (68%). This has been noted previously in patients with BJHS [30]. It is noteworthy that all lenses were stable, another helpful point of differentiation of BJHS from MFS.

Skin examination showed a median skin stretch score of two, as judged by one observer. This finding may create problems in differentiating BJHS from those forms of EDS where the skin is abnormally
stretchy. In the latter, however, the skin is velvety in texture and skin thickness is reduced [31]. In the present study, there is a strong correlation both between skin stretchiness and light transmissibility and hypermobility score. Similar significant correlations have been reported for both skin stretch and light transmissibility and hypermobility score in MFS [32].

Although bone density was reduced in patients with BJHS, particularly in those <45 yr of age, this did not reach statistical significance and no correlation was found between hypermobility scores, cardiac findings and bone density.

In conclusion, we have found that patients with BJHS do not have any significant cardiac abnormality and should be reassured accordingly. The incidence of MVP is within the normal range (7% of a control group had MVP when studied using the same equipment and criteria). There is no evidence from this study that BJHS patients have any aortic abnormalities and we find nothing to suggest that they should be followed up with regular echocardiography, as is recommended for MFS patients. Bone density may be mildly reduced, but shows no significant correlation with hypermobility score. The only significant eye abnormality was excess lid skin or laxity of lids. Conspicuously, lens dislocation was absent in all BJHS patients studied.

Thus, we have found that BJHS patients, although exhibiting features suggesting overlap with the more serious life-threatening HDCTs, do not show an increased incidence of significant cardiovascular, skin, bone or eye abnormalities, and can be reassured accordingly.

We feel that these findings will help to differentiate BJHS from other HDCTs and place patients with BJHS in a lower risk prognostic category.

REFERENCES

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