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A clinical and echocardiographic study of patients with the hypermobility syndrome

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SUMMARY Three age- and symptom-matched groups of patients with a hypermobility score of 5–9, 3–4, and 0–2 (controls), respectively, were examined for clinical and echocardiographic evidence of mitral valve prolapse and other stigmata of a collagen disorder. Mitral valve prolapse, a reduced upper segment/lower segment mitral ratio, reduced skin thickness, spinal anomalies, and a history of fracture were found to be significantly commoner among the hypermobile patients than the controls. The data suggest that the so-called hypermobility syndrome, far from being a benign locomotor disorder of healthy persons, may be a forme fruste of a hereditary disorder of connective tissue.

Generalised joint hypermobility resulting from ligamentous laxity is a feature of many hereditary disorders of connective tissue, such as the Marfan syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome.[1] The term 'hypermobility syndrome' was coined by Kirk *et al.*[2] to denote the presence of rheumatic symptoms in otherwise healthy subjects in whom generalised joint laxity is the only observed abnormality. Subsequent studies have confirmed both the association between articular and spinal complaints and hypermobility[3 4] and the hereditary nature of the ligamentous laxity, which may be inherited by both dominant and recessive modes of inheritance.[5 6]

Up to the present time the 'hypermobility syndrome' has been considered to be a benign disorder giving rise to certain articular complications such as predisposition to ligament rupture,[7] dislocations,[8] recurrent effusions,[9] Baker's cyst formation,[10] low back pain,[4] spondylolisthesis (H. Bird, personal communication), and possibly premature osteoarthrosis,[11] but not associated with disorders in other systems. In particular, evidence that it might be part of a generalised connective tissue disorder has not been forthcoming. This study sets out to explore that hypothesis.

Patients and methods

Eighty-seven patients (80 female and 7 male) attending the rheumatology clinic at Guy's Hospital with rheumatic complaints were selected and agreed to take part. Patients were excluded from the study if they showed evidence of inflammatory joint disease or if they had typical features of one of the identifiable hereditary disorders of connective tissues. Two patients with Ehlers-Danlos syndrome type I were excluded under this category. It was not possible to differentiate between the hypermobility syndrome under investigation and Ehlers-Danlos syndrome type III, in which joint hypermobility is generalised and gross while skin hyperextensibility and scarring may be minimal.[12] Patients were allocated to 1 of 3 groups matched in terms of age and presenting locomotor symptom according to their hypermobility score (HMS) on well established criteria[12] which gave a maximum score of 9 points (Table 1). Since only 7 males presented for the study, it was decided to exclude their data from the analysis. Group A comprised those female patients scoring 5–9, group B those scoring 3–4, while group C, containing female patients with a score of 0–2, acted

Table 1 *Hypermobility scoring system (after Beighton and Horan[12])*

Passive hyperextension of the 5th metacarpophalangeal joint to 90° scores 1 for each hand
Passive apposition of the thumb to the volar aspect of the forearm scores 1 for each arm
Passive hyperextension of the elbow to more than 10° scores 1 for each arm
Passive hyperextension of the knees to beyond 10° scores 1 for each leg
Placing hands flat on floor by flexing spine while maintaining knees straight scores 1
Maximum score 9

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as controls. There were 33 patients in group A, 21 in group B, and 26 in group C. All subjects were Caucasian with the exception of 3 in group A, 2 in group B, and 1 in group C.

All patients attended for a detailed clinical evaluation. Information was sought concerning past and present rheumatological and orthopaedic complaints. Measurements of height, arm span, and upper segment/lower segment (US/LS) ratio were recorded. Skinfold thickness was measured on the dorsum of the right hand overlying the third metacarpal with the Harpenden caliper.[13] In-vivo skin elasticity was also measured by the suction cup method.[14] Where available, spinal radiographs were examined, and the frequency of observed abnormalities was compared in the 3 groups of patients.

A full cardiological examination, including electrocardiography and echocardiography, was performed by a 'blind' independent observer. Auscultation of the heart was performed with the patient in the supine, left lateral, and standing positions. M-mode echocardiograms were recorded with an Ekoline 20A ultrasonoscope equipped with a 2·25 MHz transducer focused at 10 cm and an Ekoline 21 strip-chart recorder (Smith Kline Instruments). During the recording particular attention was paid to the presence or absence of echocardiographic evidence of mitral valve prolapse (MVP). The echocardiograms were analysed on a subsequent occasion under 'blind' conditions. Abrupt posterior motion of the mitral echo in mid-systole or pansystolic posterior bowing of the mitral echo of at least 3 mm in depth were taken as evidence of MVP (Fig. 1). This was classified as mild when the depth of prolapse was 4 mm or less and marked when the depth of prolapse exceeded 4 mm.

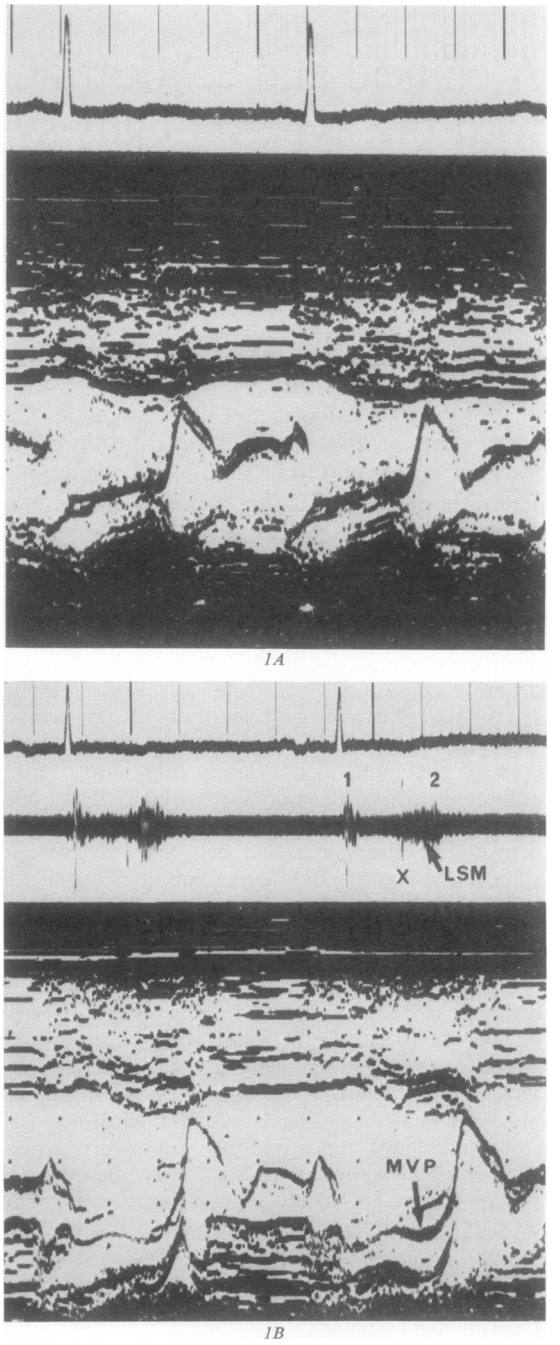
Statistical significances were determined by the chi-square method, with the exception of the skin studies, where Student's *t* test was used.

Results

The 3 groups were well matched in respect of age and presenting symptom (Table 2). Low back pain was slightly more prevalent and joint problems less frequent in the control group, but these differences did not achieve statistical significance.

ASSOCIATED SYMPTOMS

Other symptoms of a rheumatological nature or suggestive of a connective tissue disorder are shown in Table 3. Some of these—effusions, muscle cramps, easy bruising, and varicose veins—were common in all 3 groups and appeared with approximately



1A

1B

Fig. 1 *A, a normal mitral echogram and, B an echocardiogram from one of our hypermobile patients with MVP, seen as abrupt posterior movement of the mitral echo in mid systole. The mid systolic click (x) and late systolic murmur (LSM) are shown on the simultaneous phonocardiogram.*

Table 2 *Patient characteristics and presenting symptoms*

Group:	*A*	*B*	*C (Controls)*
Hypermobility score:	*HMS 5–9*	*HMS 3–4*	*HMS 0–2*
Number	33	21	26
Mean age (range)	38 (19–64)	38 (22–61)	46 (23–70)
Back pain	73%	76%	81%
Joint problems			
Osteoarthritis	24%	19%	23%
Arthralgia	58%	67%	42%
Total	82%	86%	65%

Table 3 *Clinical features*

Incidence of history of	*Group A HMS 5–9*	*Group B HMS 3–4*	*Group C controls HMS 0–2*
Fracture	17/33 (52%)**	3/21 (14%)	4/26 (15%)
Dislocation	5/33 (15%)	1/21 (5%)	1/26 (4%)
Raynaud's phenomenon	7/33 (21%)	2/21 (10%)	2/26 (8%)
Capsulitis	5/33 (15%)	1/21 (5%)	1/26 (4%)
Effusions	10/33 (30%)	4/21 (19%)	10/26 (38%)
Muscle cramps	17/33 (52%)	11/21 (52%)	8/26 (31%)
Calf swelling	3/33 (9%)	1/21 (5%)	2/26 (8%)
Ligament injuries	16/33 (48%)*	10/21 (48%)*	6/26 (23%)
Epicondylitis	5/33 (15%)	1/21 (5%)	4/26 (15%)
Carpal tunnel syndrome	2/33	1/21	2/26
Muscle tear	4/33	0	1/26
Poor skin healing	2/33	2/21	2/26
Bruising	24/33 (73%)	14/21 (67%)	16/26 (62%)
Varicose veins	5/33 (15%)	6/21 (29%)	6/26 (23%)

Compared with controls: **$p<0.01$, *$p<0.05$.

equal frequency in all of them. Others—a history of dislocation, Raynaud's phenomenon, shoulder capsulitis, and muscle tears—were more frequent in the hypermobile groups than in the controls, but the differences were not significant. A history of previous fracture was found in 52% of patients in group A compared with only 15% in the controls—a highly significant difference ($p<0.01$). A significant increase in the incidence of ligament injuries was seen in both hypermobile groups A and B as compared with controls ($p<0.05$).

SPINAL X-RAYS

Spinal anomalies including scoliosis, transitional vertebrae at the lumbosacral junction, and pars interarticularis defects with or without spondylolisthesis were present in 11 (73%) out of 15 patients *x*-rayed in group A, in 3 (33%) out of 9 *x*-rayed in group B, and in only 3 (23%) out of 13 *x*-rayed in group C. Differences between group A and the controls were significant ($p<0.01$) (Table 4). None of the controls had a spondylolisthesis or a pars defect.

Table 4 *Spinal anomalies*

Group	*X-rayed*		*Those x-rayed and having anomalies*	
	No.	*%*	*No.*	*%*
Group A (HMS 5–9)	15/33	45%	11/15	73%*
Group B (HMS 3–4)	9/21	43%	3/9	33%
Group C controls (HMS 0–2)	13/26	50%	3/13	23%

*$p<0.01$.

CARDIOLOGICAL FINDINGS (Table 5)

The systolic click of mitral valve prolapse (MVP) was heard in 18% of patients in group A, 17% in group B, and in only 1 case (6%) in group C. A mitral regurgitant murmur was heard in 9% and 17% in groups A and B respectively and in no case in group C.

Echocardiographic findings in the 3 groups are detailed in Fig. 2 and Table 5. Both hypermobile groups (A and B) showed a significantly greater prevalence of MVP than the control group, C. Measurements of left atrial depth and aortic root diameter from the echocardiograms were not significantly different in any of the 3 groups. Left atrial depth exceeded the normal range in 2 patients from each group. There was a trend towards a positive correlation between anterior mitral leaflet excursion (MVE) and hypermobility score but this did not reach statistical significance ($r=0.23$, $p>0.05$).

Abnormal resting electrocardiograms were recorded in 7 patients, 5 of whom had MVP. In group A 5 patients had abnormal ECGs compared with only 1

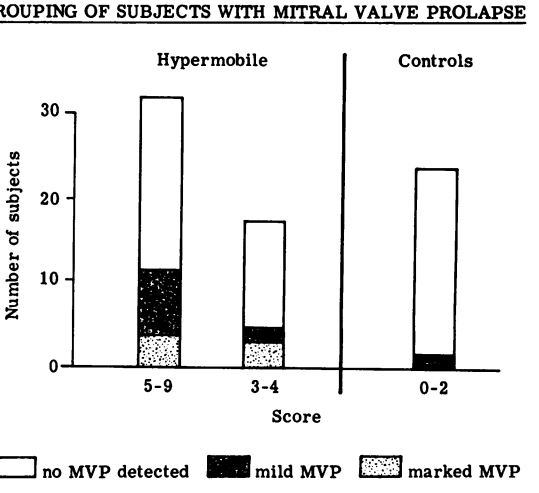


Fig. 2 *The incidence of mild (hatched) and marked (stippled) MVP in the different hypermobility groups.*

Table 5 *Cardiological findings*

	Patients		*Controls*
Hypermobility score	5–9	3–4	0–2
Click	6/33 (18%)	3/18 (17%)	1/25 (4%)
Murmur	3/33 (9%)	3/18 (17%)	0/25
Echocardiographic evidence of MVP			
Marked	4/33 (12%)	3/18 (17%)	0/25
Mild	8/33 (24%)	2/18 (11%)	2/25 (8%)
Total	12/33** (36%)	5/18 (28%)**	2/25 (8%)
Mean left atrial depth cm ± SD (normal range 1·9–3·8 cm)	3·0 ± 0·5	3·0 ± 0·6	3·1 ± 0·5
Mean mitral valve excursion, cm ± SD (normal range 1·8–2·5)	2·1 ± 0·3	2·0 ± 0·3	1·9 ± 0·3
Aortic diameter cm ± SD (normal range 2·0–3·7)	2·8 ± 0·4	2·7 ± 0·3	2·8 ± 0·3
Electrocardiographic abnormalities—RBBB	1	0	0
1st Degree heart block	1	0	0
Inferolateral ST sagging	1	1†	0
Frequent ventricular ectopic beats	1	1†	1
Abnormal QRS axis (−30°)	1	0	0
Total abnormal ECG	5/29* (17%)	1/18 (6%)	1/16 (6%)

**p<0·02, *p<0·05. †Same patient. RBBB = right bundle branch block.

patient in each of the other groups. Details of the ECG abnormalities are summarised in Table 5.

BODY HABITUS

The numbers of patients showing a US/LS ratio of less than 0·89 in the 3 groups are shown in the histogram (Fig. 3). With groups A and B taken together the incidence of low US/LS ratio was 21 out of 54 (39%) compared with 3 out of 26 (11·5%) in the control group C (p<0·05).

SKIN STUDIES

For the skin thickness and elasticity studies patients were carefully selected to achieve the closest possible matching of the 3 groups in respect of age and presenting symptoms. In this way it was possible to select 3 matched groups each containing 16 patients. Results are given in Table 6. It will be seen that with regard to skin thickness there was a trend towards an inverse relationship between hypermobility scores and skin thickness; the difference between group A (HMS 5–9) and the control group (HMS 0–2) achieved statistical significance (p<0·02). In contrast, there were no appreciable differences in skin elasticity between the 3 groups.

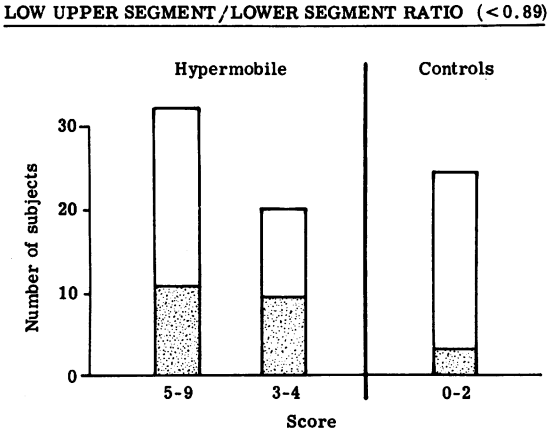


Fig. 3 *The incidence of reduced US/LS ratio (less than 0·89) in the different hypermobility groups.*

Table 6 *Skin thickness and skin elasticity*

HMS patients			*Matched controls*
HM score	5–9	3–4	0–2
Number	16	16	16
Skin thickness in cm (± SEM)	0·098* (± 0·0026)	0·102 (± 0·0027)	0·11 (±0·002)
Skin elasticity PA × 10^{-7} (± SEM)	1·94 (± 0·26)	2·25 (± 0·27)	2·04 (± 0·24)

*p<0·02.

CORRELATION BETWEEN OBSERVED ABNORMALITIES

Both arthralgia and a history of fracture were more frequent among patients with MVP in hypermobile groups A and B than in those without MVP in the same group, the difference being significant (p<0·05) in respect of group A only. Thus arthralgia was seen in 83% of those patients in group A with MVP and in only 43% of those without it. In group B the corresponding figures were 80 and 69% respectively. For fractures the incidences in group A were 75% and 38% with and without MVP respectively. Corresponding figures for group B were 20% and 0.

Soft tissue lesions including epicondylitis, carpal tunnel syndrome, and tenosynovitis were more common in both hypermobile groups in patients with MVP than in those without it. The numbers, however, were small, and statistically significant trends were not seen. Lower US/LS ratios did not correlate with MVP in the hypermobile patients in either group. Unlike arthralgia, low back pain showed no association with MVP among the hypermobile patients.

Skin thickness correlated inversely with hypermobility score and also with age but not with US/LS ratio.

Discussion

Systolic prolapse of the mitral valve is a recently recognised entity.[15 16] Its clinical hallmark is a non-ejection systolic click, with or without a late systolic murmur, but in some patients it is clinically 'silent' and in others a pansystolic murmur may be present without a click. In clinical and echocardiographic studies MVP has been observed in 6·3% of 1169 healthy young females (17), and Brown *et al.* (18) found it is less frequent in males (0·5%) than in females (6%). The cause is believed to lie in defective or deficient collagen in the mitral leaflets[19] leading to leaflet expansion and chordal elongation. MVP has been described in patients suffering from various hereditary disorders of connective tissue such as the Marfan syndrome, [20 21] the Ehlers-Danlos syndrome, [22 23] and osteogenesis imperfecta,[24] but not as yet in the hypermobility syndrome,[2] which has hitherto been regarded as a benign disorder of the locomotor system affecting double-jointed but otherwise healthy persons.

A reduced skin thickness in the presence of a normal elastic modulus has been recorded in studies involving age- and sex-matched controls in both the Ehlers-Danlos syndrome[25] and osteogenesis imperfecta.[26] To the best of our knowledge no previous studies have been undertaken in patients with the hypermobility syndrome. Although increased *extensibility* of collagenous tissues is considered to be a cause of abnormalities such as joint laxity, kyphoscoliosis, floppy heart valves, and stretchy skin,[27] our measurements of skin elasticity in these patients revealed no abnormality. *Fragility* of the collagen framework, however, could well account for the skeletal and cardiac abnormalities we have found. Fragility could reflect a quantitative decrease in collagen content of the tissues—as suggested by the reduced skin thickness—or a qualitative difference in the connective tissue architecture. This in turn could reflect a molecular defect in collagen, as is suggested by the recent observation of an increase in procollagen in floppy mitral valves.[28]

In the present study rheumatic patients with soft tissue or degenerative lesions were selected on the basis of their hypermobility score into 1 of 3 groups closely matched for age and presenting complaint. Since only 7 males (9%) of those with an HMS presented themselves during the period of study (an observation in itself not without interest, particularly in relation to the reported sex distribution of MVP), it was decided to exclude them from the analysis. Also excluded were patients with an inflammatory joint disease and those considered to be suffering from one of the identifiable hereditary disorders of connective tissue. Two patients with the Ehlers-Danlos syndrome were excluded under this category. The remainder constituted 3 age- and symptom-matched groups; 2 (groups A and B with an HMS of 5–9 and 3–4 respectively) were diagnosed as suffering from the hypermobility syndrome and a third, group C, with an HMS of 0–2 acting as a control group.

The results show the increased prevalence of MVP, a reduced US/LS ratio, a reduced skin thickness, spinal anomalies, and a history of fracture among hypermobile subjects. These findings suggest that patients may have a collagen defect that is manifested not only in joint laxity but also in abnormalities in heart valves, skin, and bone. Furthermore, there appears to be an association with a marfanoid habitus as shown by the reduced US/LS ratio. The apparent occurrence of a generalised connective tissue defect in patients with the 'hypermobility syndrome' highlights the difficulty of differentiating between these patients and those with the milder forms of the Ehlers-Danlos syndrome. Indeed, we conclude that the so-called hypermobility syndrome may be a forme fruste of a hereditary disorder of connective tissue.

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