Clinical Study of Hereditary Disorders of Connective Tissues in a Chilean Population

Joint Hypermobility Syndrome and Vascular Ehlers-Danlos Syndrome

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Objective. **To demonstrate the high frequency and lack of diagnosis of joint hypermobility syndrome (JHS) and the seriousness of vascular Ehlers-Danlos syndrome (VEDS).**

Methods. **Two hundred forty-nine Chilean patients with hereditary disorders of the connective tissues (CTDs) and 64 control subjects were evaluated for the diagnoses of JHS and VEDS using the validated Brighton criteria, as compared with the traditional Beighton score. In addition, the presence of blue sclera was determined, with the degree of intensity graded as mild, moderate, or marked.**

Results. **The frequency of hereditary CTDs was 35%, with diagnoses of JHS in 92.4% of subjects, VEDS in 7.2%, and osteogenesis imperfecta in 0.4%. The Beighton score proved to be insufficient for the diagnosis of JHS (35% of subjects had a negative score), whereas the Brighton criteria yielded positive findings (a diagnosis of JHS) in 39% of control subjects. Blue sclera was frequent, being identified in 97% of JHS patients and 94% of VEDS patients. Moderate osteopenia/osteoporosis was observed in 50% of patients with VEDS and 26% of those with JHS. Dysautonomia, dyslipidemia, and scoliosis were more frequent in VEDS patients than in JHS patients. The typical JHS facial appearance and the "hand holding the head sign" were identified. Raynaud's phenomenon was extremely rare in JHS patients (2%). Ruptured uterus and cerebral aneurysm occurred in 12% and 6% of VEDS patients, respectively. Spontaneous pneumothorax was more frequent in VEDS patients (11%) than in JHS patients (0.9%).**

Conclusion. **JHS is very frequent but usually undiagnosed. The Beighton score is an insufficient method for JHS diagnosis. We recommend that physicians learn to recognize the typical facial features of JHS and be able to identify blue sclera. We also propose that validated hypermobility criteria be routinely used. Further research is needed to determine why the prevalence of JHS is so high in Chile.**

Hippocrates first described hypermobile joints 2,400 years ago, but the condition of joint hypermobility was not described as a medical problem until 1967, by Kirk et al (1). Although many people have hypermobile joints, the general public as well as many physicians consider hypermobility to be a curiosity rather than a potentially serious medical problem (2,3). The prevalence of hypermobility is difficult to evaluate because it varies with age, sex, and ethnic background and because multiple criteria are being used. It is more frequent in female subjects and children, is more frequent in Asian than in black populations, and is more frequent in both Asian and black populations than in whites. It is generally agreed that it exists in ~10% of individuals in Western populations (4) and up to 25% in Iraqis (5). Most cases of joint hypermobility are pauciarticular rather than generalized, which makes the diagnosis more difficult. Because of this, many people are unaware of having lax joints (6). In spite of this laxity in the joints, most people with hypermobility do not experience joint or musculoskeletal pain.

Joint hypermobility syndrome (JHS) is defined as hypermobility of the joints in conjunction with symptoms. The criteria of the Beighton score (7) were the

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first used to recognize hypermobility, and this method has been in use for 30 years. The Beighton score involves evaluation of only a few joints and does not include other involved systems. Hereditary disorders of the connective tissues (CTDs) are attributable to a generalized genetic alteration of the collagen fibers, and most tissues can be affected, as evidenced by the presence of a variety of articular and nonarticular signs and symptoms. The classic forms of hereditary CTDs include, among others, Marfan syndrome (MFS), vascular Ehlers-Danlos syndrome (VEDS), and osteogenesis imperfecta (OI). These conditions are rare (8), with a range of frequency of 1 in 5,000 for EDS, 1 in 12,000 for MFS, and 1 in 100,000 for OI. In fact, the number of EDS subtypes has been reduced from 10 to 6.

The low frequency of the classic hereditary CTDs would explain why, in our clinic, we have seen only 1 patient with MFS and only 1 with OI. We have not seen any cases of EDS type VI (oculo-scoliotic) among our patients. Moreover, we have seen only 2 patients with the classic-type EDS (formerly, types I and II) (not included in this study), which are characterized by significant fragility of the skin, atrophic scars, and extreme joint laxity (9). Some patients with hereditary CTDs have a predominance of vascular problems, while others have osteoporosis, but all of them share the feature of joint hypermobility, which ranges in severity. Most authors believe that JHS is the same condition as the Ehlers-Danlos hypermobility syndrome, previously called EDS type III, and that it is a forme fruste of the latter hereditary CTD since it has many features of EDS, MFS, and OI, but to a lesser degree (2). There is considerable overlap between the clinical features of all of these conditions. According to some investigators (for example, Masi A: personal communication), JHS is a polymorphic variant in the hereditary CTD population.

Hereditary CTDs are manifested by alterations of the extracellular matrix of the connective tissues. It is known that almost 195 proteins are involved in connective tissue metabolism. Mutations in the genes that encode these proteins can cause more than 200 hereditary CTD conditions (9). The knowledge that patients with JHS can have serious problems in other systems in addition to the joints resulted in the revision of the Beighton score. The reason for this systemic involvement is that collagen is an important part of most tissues.

In 1998, Grahame et al (10) presented the validated diagnostic criteria for JHS known as the Brighton criteria. These criteria include not only hypermobility of the joints (also recognized by the Beighton score), but also take into consideration alterations in other tissues. Use of the Brighton criteria has facilitated the detection of patients with JHS who usually go undiagnosed in most parts of the world. Guma et al reported a frequency of hypermobility in 25% of patients in a rheumatology clinic in Spain (11). In 2000, JHS was diagnosed in 35% of the patients seen in our rheumatology unit (12). Grahame noted that JHS is probably the most frequent cause of pain reported in rheumatologic practice in the UK (33%) and is rarely diagnosed. Moreover, Grahame suggested, and we agree, that physicians do not give this condition its proper importance (2).

Since JHS has autosomal dominant inheritance, we need to consider this diagnosis if the patient has a family member with similar problems. There are no biochemical or genetic markers to confirm the diagnosis. In contrast, VEDS can be confirmed by biochemical or molecular analysis (13). However, in MFS, in spite of the existence of a genetic fibrillin 1 alteration at 15q21, its diagnosis continues to be based on clinical features (14). In general, genetic alterations of collagen fiber predispose an individual to pain and instability of the joints, with a tendency to develop early osteoarthritis, early osteoporosis, and complications in many other tissues attributable to collagen fragility. Because of these multiple problems as well as chronic pain and fatigue, and because treatment is often ineffective, patients frequently have associated anxiety and fear, and, sometimes, depression. These patients can also have genetically determined phobias and panic crisis, as described by Bulbena et al (15,16).

VEDS is characterized by ecchymoses and vascular problems and can produce not only cerebral aneurysms or arterial rupture, but also other serious complications such as spontaneous pneumothorax, rupture of the colon, or rupture of the gravid uterus. Pope et al noted that this condition was attributable to the absence or reduction of type III collagen, which is an essential component of distensible organs such as the arteries, gut, uterus, or lung, resulting in wear and tear of such organs and rupture in early adult life (17). For this reason, it is imperative to clinically determine whether the patient has family members with JHS or VEDS.

The purpose of the present study was to increase awareness of JHS, as well as its associated chronic morbidity and poor quality of life, and to demonstrate the high frequency of JHS as compared with the less frequent, but more dangerous, VEDS. It is important to point out that both of these conditions usually go undiagnosed. JHS is not as benign as it was first thought, due to the fragility of many tissues, and it may produce severe complications such as poor cicatrization, recur-

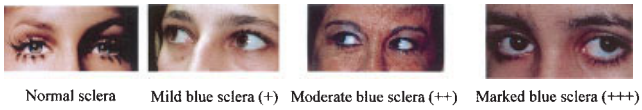

Figure 1. Blue sclera in patients with joint hypermobility syndrome (see ref. 21).

rent arthralgias, tendinitis, subluxations, early disc disease, early myopia, early varicose veins, hernias, genital or rectal prolapse, and even spontaneous pneumothorax. It can also produce early osteoarthritis, early osteoporosis, dysautonomia, and dyslipidemia.

PATIENTS AND METHODS

Two hundred forty-nine consecutive patients with hereditary CTDs were studied over a period of 2 years, starting in January 2001, in the rheumatology office of a private clinic in Santiago, Chile. They constituted 35% of the 712 patients seen in that period. Nineteen patients with concomitant arthritis were excluded from the study. A total of 64 adult subjects who were medical and paramedical personnel constituted the control group. We defined each classic hereditary CTD (MFS, EDS, and OI) using the standard criteria reported in the literature (14,18,19,20). In cases of overlap between VEDS and JHS, we classified them as VEDS.

All patients and controls were evaluated by the same examiner (JFB), using the Brighton criteria for diagnosis. For one of the criteria, we used the term marfanoid habitus as

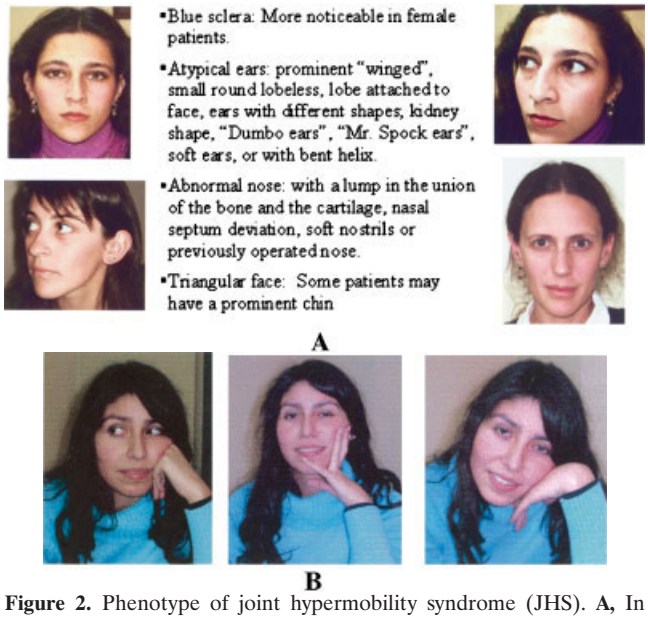

Figure 2. Phenotype of joint hypermobility syndrome (JHS). **A,** In addition to the listed typical facial characteristics of JHS (21), other features that have been described previously are drooping eyelids and antimongoloid slant, as noted in the Brighton criteria. **B,** "Hand holding the head" is another sign of JHS.

defined by the Brighton criteria (10). Criteria were applied according to the following definitions. 1) For dysautonomia, we included a patient if he or she had at least 3 of the following

Table 1. Comparison of joint mobility and affected tissues between patients with joint hypermobility syndrome (JHS), patients with vascular Ehlers-Danlos syndrome (VEDS), and controls, using the Brighton criteria for diagnosis*

	Controls (n = 64)	JHS (n = 230)	VEDS (n = 18)†	*P* Control vs. JHS	*P* JHS vs. VEDS
Major criteria‡					
1. Major criteria 1	16 (25)	83 (36)	3 (17)	NS	NS
2. Major criteria 2	2 (3)	14 (6)	1 (6)	NS	NS
Minor criteria‡					
1. Beighton score ≤3 of 9	44 (69)	126 (55)	14 (78)	NS	NS
2a. Arthralgias§	17 (27)	130 (57)	9 (50)	<0.01	NS
2b. Back problems	25 (39)	140 (61)	13 (72)	<0.01	NS
3. Subluxations	8 (13)	59 (26)	0 (0)	<0.05	<0.01
4. Recurrent tendinitis	12 (19)	121 (53)	4 (22)	<0.01	<0.01
5. Marfanoid habitus	3 (5)	33 (14)	2 (11)	<0.05	NS
6. Skin abnormalities	61 (95)	216 (94)	18 (100)	NS	NS
7. Myopia	9 (14)	18 (8)	2 (11)	NS	NS
8a. Varicose veins	11 (17)	47 (20)	6 (33)	NS	NS
8b. Hernias/prolapse	4 (6)	28 (12)	5 (28)	NS	NS

* Values are the number (%) of subjects satisfying the criteria (11). NS = not significant.
† VEDS is an exclusion criterion in the Brighton criteria.
‡ Major criteria 1 requires a Beighton score of ≥4 of 9 possible joints. Major criteria 2 requires the presence of arthralgias in >3 joints lasting >3 months. The Brighton criteria major 1 and minor 1 are mutually exclusive, as are major 2 and minor 2.
§ In 1–3 joints, for >3 months.

Table 2. Frequency of signs and symptoms not included in the Brighton criteria*

	JHS (n = 230)	VEDS (n = 18)	*P*
Blue sclera (+, ++, +++)	222 (97)	17 (94)	NS
Flat foot	69 (30)	14 (78)	<0.01
Osteopenia and osteoporosis†	60 (26)	9 (50)	<0.05
Dysautonomia	53 (23)	7 (39)	<0.01
Dyslipidemia	28 (12)	6 (33)	<0.01
Scoliosis	28 (12)	6 (33)	<0.01
Nasal cartilage abnormality	41 (18)	4 (22)	NS
Early osteoarthritis	12 (6)	2 (11)	NS
Raynaud's phenomenon	5 (2)	2 (11)	NS

* Values are the number (%) of subjects. See Table 1 for definitions.
† Both moderate and severe osteopenia were considered.

symptoms: tiredness/sleepiness, chronic fatigue, dizziness/occasional syncope, marked cold intolerance, or inability to stand for some time without moving the feet (the tilt table test was not regularly performed). 2) For dyslipidemia, we included a patient if 1 of the following features was present: significant alteration in serum cholesterol level, elevated triglycerides, or current treatment for dyslipidemia. 3) For nasal cartilage abnormality, we included a patient if he or she had 1 of the following criteria: presence of a nodule at the union of the bone and cartilage on the dorsum of the nose, deviation of the nasal cartilage, or previous surgery on the nose for aesthetic reasons (with exclusion of trauma).

The frequency of blue sclera in the Chilean general population was evaluated in a group of 70 white subjects whose mean age and sex proportions were similar to those of the control group. We used our already published grading system (21) to evaluate the degree of intensity of blue sclera (Figure 1). This was as follows: + = mild intensity, distinguishable only at close examination; ++ = moderate intensity, identifiable from across the table; +++ = marked intensity, identifiable at a distance of 4–5 meters. The results were analyzed statistically with the chi-square and Fisher's exact tests.

RESULTS

The study comprised 249 patients with hereditary CTDs, distributed as follows: JHS 92%, VEDS 7%, and OI 0.4%. The age range of the JHS patients was 13–84 years, with a median of 45 years, similar to that of the 64 control subjects (age range 13–80 years, median age 43 years). VEDS patients had a median age similar to that of the JHS patients (median age 47 years, age range 31–70 years) and were a little older than the controls. Of the 249 patients, 80.3% were women; more VEDS patients than JHS patients were women (94% versus 79%).

Among the control subjects, 23% had positive diagnostic findings by the Beighton score, and 39% had positive findings by the Brighton criteria. We compared the frequency of a positive Beighton score in controls with that in JHS and VEDS patients, and found that 65% of JHS patients had a positive score and 17% of VEDS patients had a positive score ($P < 0.05$). As stated in the literature (20), VEDS patients were shown to have less severe hypermobility of the joints compared with JHS patients. There were significant differences in hypermobility between JHS patients and controls in only the metacarpophalangeal (MCP) joints and hands placed flat on the floor.

Thirty-nine percent of controls had positive diagnostic findings by the Brighton criteria ($P < 0.0001$). Using these criteria, Table 1 shows a comparison of the frequency of signs and symptoms seen in both conditions with that seen in the controls. Subluxations and recurrent tendinitis were significantly more frequent in JHS patients than in VEDS patients. Marfanoid habitus was seen in 14% of JHS patients. Skin abnormalities were seen in almost all patients and all controls; some of these were nonspecific, but others were typical, such as soft, lax, velvety skin and poor cicatrization (cheloids and papyraceous scars). The frequency of hernias and uterine or rectal prolapse was low in JHS and VEDS patients (12% and 28%, respectively), but was higher in both patient groups than in controls (6%).

In our evaluations, we noted the typical facial appearance of JHS (Figure 2A) and the "hand holding the head sign" (Figure 2B). This included marked flexion of the MCP and wrist joints, and hyperextension of the fingers when holding the head during the interview. Severe complications observed in the patients were cerebral aneurysm in 1 of 18 VEDS patients (6%), spontaneous pneumothorax in 2 of 230 JHS patients (0.9%) and in 2 of 18 VEDS patients (11%), and gravid uterus rupture in 2 of the 17 VEDS patients evaluated (12%).

Other findings were blue sclera (Figure 1), flat

Table 3. Blue sclera and hypermobility in control subjects*

	Total (n = 70)	Men (n = 18)	Women (n = 52)
Sex		26	74
Mean age, years	40	46	38
Age range, years	13–77	27–77	13–66
Total with blue sclerae	43	17	52
Intensity of blue sclerae			
+	33	17	39
++	10	0	14
+++	0	0	0
Total with joint hypermobility†	49	33	54

* Except where indicated otherwise, values are the % of subjects.
† Ability to extend the fifth finger to 90° or more.

foot, moderate and severe osteopenia and osteoporosis, dysautonomia, dyslipidemia, scoliosis, nasal cartilage abnormality, early osteoarthritis, and Raynaud's phenomenon (Table 2). Blue sclera was present in almost all of the JHS patients (97%) and VEDS patients (94%). Among the controls (Table 3), blue sclera was identified in 43% of subjects ($P < 0.05$).

DISCUSSION

The most probable explanation for the very high proportion of positive findings by the Brighton criteria in controls is that, indeed, in the population studied there were a high number of patients with JHS (39%) who have not been diagnosed. Since this is not a well-known condition, people and physicians are unaware of its presence.

Most authors agree that JHS has autosomal dominant inheritance, but in many cases the disease appears as a result of mutations observed in one family. No specific mutation has so far been found for JHS. Mutations in COL3A1 result in vascular-type EDS. Recently, Zweers et al (22–24) suggested that a Tenascin-X mutation could well be a candidate for joint hypermobility. Those authors believe that complete or partial deficiency (haploinsufficiency) of Tenascin-X can result in 2 distinct hereditary CTDs in which hypermobility is present, indicating that Tenascin-X has an essential role in the mechanical properties of skin, ligaments, and tendons (23).

We have proposed a theory (25,26) that a lack of folic acid during the periconception period could, by altering genetic DNA, produce a weaker collagen, similar to what happens in neural tube defects. The fact that JHS has a higher prevalence in Chile and probably also in other Latin populations could be attributable to the higher frequency of polymorphisms of methylenetetrahydrofolate reductase in these populations (40%) compared with that in most other communities (10–20%) (27–29). This polymorphism reduces the enzyme activity by 50%, thus increasing the folic acid requirement. Reinforcing our theory, Lucock recently demonstrated that elevated homocysteine levels due to a lack of folic acid can chelate copper, thus changing its properties, and can inhibit the lysyl oxidase enzyme, which alters the collagen and elastin links, producing weakness of the collagen tissues (30). This also appears to be important in the pathogenesis of the osteoporosis seen in patients with hereditary CTDs. Recent population studies done in Framingham, Massachusetts (31) and Rotterdam, The Netherlands (32), with more than 2,000 patients in each, showed the predictive value of homocysteine levels as a fracture risk in osteoporosis. In Japan, Sato et al (33) showed a statistically significant reduction of hip fracture after treatment with folic acid and vitamin B12 when compared with placebo in 628 patients with hemiplegia secondary to stroke.

When included in the clinical evaluation, JHS is a very frequent diagnosis made in rheumatologic consultation worldwide (35%). However, it is even higher in our practice (80%), since we have become a referral center for these conditions (34). JHS patients with arthralgias often receive a wrong diagnosis. We consider it important to emphasize that it is possible to have JHS or VEDS in association with other rheumatic conditions. Knowing how to diagnose these patients helps to avoid diagnostic confusion. It is interesting that in some cases, we had difficulty in the differential diagnosis of pelvispondylarthropathy (PEA) and JHS. The former is characterized by musculoskeletal stiffness, whereas JHS has the feature of hypermobility. The problem arises in that both conditions can manifest with chronic back pain, chondrocostal pain, and joint stiffness, in conjunction with inactivity, enthesitis, and arthralgias. In a study of patients with hereditary CTDs, we found that bone scintigraphy was a useful technique for diagnosing JHS, but not for the differential diagnosis of PEA (35). Since chronic pain, chronic fatigue (dysautonomia), and "trigger points" (enthesitis) are features of both fibromyalgia (FM) and JHS, it is our opinion that many patients diagnosed as having FM could indeed have JHS.

The JHS group included 14% of patients with marfanoid habitus. We mainly see patients with JHS and only a few patients with other types of EDS, because JHS is extremely frequent and also because of the referral pattern in our rheumatology practice. Patients are referred to us mainly because of the symptoms of arthralgias, tendinitis, bursitis, back pain, osteoporosis, and hypermobility. Cardiologists and vascular surgeons will evaluate patients with MFS and VEDS when vascular complications are present. Patients with OI are seen mainly by traumatologists, and only because fractures are present.

The facial appearance typical of VEDS is well known (18). We have previously described the typical facial appearance of JHS (21) (Figure 2A), which has helped us to recognize the diagnosis of JHS. The facial characteristics of VEDS and JHS have some similarities, but with experience, they are easily distinguishable. Patients with VEDS have sunken eyes, a thin upper lip, and lack of facial fatty tissue. Both conditions can be characterized by a triangular face. We have also found

that observing the way patients hold their head with the hand, during the interview, facilitates the diagnosis of JHS; we have termed this the "hand holding the head sign" (Figure 2B). VEDS is fairly infrequent, and in this study, only 7% of the patients were diagnosed as having VEDS, including 6 who belonged to the same family. Since these are hereditary diseases, patients with JHS or VEDS at any age were evaluated. Both conditions were seen more frequently in female subjects.

As stated in the literature, the Beighton score (10) by itself proved to be insufficient for the diagnosis of JHS, since a positive Beighton score was present in only 65% of JHS patients and in 17% of VEDS patients. As is already known (36), VEDS patients were shown to be less hypermobile than JHS patients; they had a higher percentage of negative Beighton scores (83%) compared with JHS patients (35%), and this difference was statistically significant ($P < 0.05$). If we consider that most Western countries have a frequency of hypermobility of 10% (4), the fact that 23% of normal controls in this study had a positive Beighton score indicates a higher prevalence of hypermobility. This was further noticeable with the finding that 39% of these controls were positive by the Brighton criteria, indicating a high prevalence of undiagnosed JHS in the control group.

Despite the fact that the Brighton criteria have been criticized because of lack of reliability, we used it with the idea that it had already been validated by Grahame et al (10) for people older than age 16 years, and with the intention that it would be easier for comparison with the findings of other studies, since these criteria are widely used. There are other very reliable diagnostic methods, including the Rotes criteria (37) and the Hospital del Mar (Barcelona) criteria. Bulbena et al added 6 more areas of study to these criteria, creating a more complete joint evaluation (38). These criteria have a different cutoff point for women and men, since women tend to have more positive signs than do men. These more complete and validated criteria have been used extensively in Latin countries and in studies from Spain.

In Table 1, we did not separate men and women when applying the Brighton criteria, because the VEDS group had 17 women and only 1 man, whereas in the JHS group, 79% were women. We also did not separate the subjects by age, which is another factor in laxity, because 92% of the JHS patients and 100% of the VEDS patients were older than age 20 years.

When comparing joint mobility between the control group, the patients with JHS, and the patients with VEDS, we found that the most mobile joints in all groups were the MCPs and the hands laid flat on the floor. As expected, these mobile joints were significantly more frequent in JHS patients than in controls. Table 1 shows a comparison of the signs and symptoms seen in the controls, JHS patients, and VEDS patients, recognized by applying the Brighton criteria. Subluxations and recurrent tendinitis were significantly more common in the JHS patients as compared with the VEDS patients. Moreover, these symptoms, in addition to arthralgias, back problems, and marfanoid habitus, were more significant in the JHS patients than in the controls. The percentage of adolescents with marfanoid habitus has increased in Chile and in other parts of the world; this is interesting, since this body habitus constitutes a minor criterion of the Brighton criteria. The reason to include this feature in the Brighton criteria is that subjects with marfanoid habitus have JHS, with their usual signs and symptoms, including early osteoporosis. The incidence of hernias and uterine or rectal prolapse was low in both the JHS and the VEDS patients (12% and 28%, respectively), but higher than in controls (6%), probably because of tissue fragility.

It is well known that patients with hereditary CTDs may have osteoporosis, but this problem has not been well studied in JHS. It is important to note that low bone mineral density was encountered quite frequently both in the JHS patients (26%) and in the VEDS patients (50%). Densitometry is usually not requested in young patients. We have seen osteoporosis in male and female subjects as young as 13 years old.

We identified early osteoarthritis in 6% of JHS patients and 11% of VEDS patients. We agree with other authors in that, in general, osteoarthritis is more frequent and occurs at an earlier age in patients with hypermobility; some have seen osteoarthritis occur in up to 60% of patients compared with 30% of controls (39,40). Chronic joint instability and altered collagen in cartilage are possible causes of early degenerative joint disease in these patients. One exception is osteoarthritis of the proximal interphalangeal joints, in which, as noted by Kraus et al (41), hypermobility appears to be protective.

Autonomic nervous system (ANS) imbalance appears frequently in these patients, causing palpitations, arrhythmias, and dysautonomia. We found that dysautonomia was frequent both in the JHS patients (23%) and in the VEDS patients (39%). Dysautonomia is a difficult term to define. The problem is that there is no definite agreement on how to study the ANS. A recent European survey revealed the difficulty in interpreting results from so many different diagnostic tests, in which

different equipment and different laboratory methods are used (42). The upright tilt table test was not regularly done, since it is not practical and does not provide a definite diagnosis (it has a sensitivity of 75% and specificity of 88–93%) (43). We suggest that in future studies, a more objective evaluation of dysautonomia be used, such as the heart rate variability analysis, probably with the use of a modified tilt table test or other tools to evaluate the performance of the ANS. Rowe et al (44) reported orthostatic intolerance and chronic fatigue syndrome associated with EDS. Gazit et al studied 48 JHS patients and 30 controls and found orthostatic hypotension and postural orthostatic tachycardia syndrome in 78% of the JHS patients and 10% of the controls (45). It is important to detect dysautonomia, since it appears frequently in these patients, is very distressing, produces bad quality of life (hypotension, dizziness, chronic fatigue), and is amenable to treatment.

Although we did not tabulate xerophthalmia and xerostomia, we saw these features frequently in our patients, causing confusion with Sjögren's syndrome (SS). Recently, cardiovascular autonomic dysfunction in primary SS has been reported (46). Therefore, most likely in JHS as well as in primary SS, the decreased stimulation by the ANS of the salivary and lacrimal glands would produce xerophthalmia and xerostomia. Dyslipidemia and scoliosis occurred significantly more frequently in the VEDS patients (33%); these features were also seen in JHS patients, but with a lower frequency (12%). Flat foot, usually anterior flat lax foot, was significantly more frequent in VEDS patients (78%) as compared with JHS patients (30%). Abnormal nasal and ear cartilage is part of the typical facial appearance of JHS, as described by us (25). Nasal abnormalities are nonspecific, and in this study, we saw them in 18% of JHS patients and 22% of VEDS patients. Raynaud's phenomenon was extremely rare in JHS (2%); if present, it is necessary to rule out cryoglobulinemia or an associated arthritis, such as sclerodermia, systemic lupus erythematosus, or mixed CTD. In VEDS, Raynaud's phenomenon was slightly more frequent (11%). Although they were not recorded, acrocianosis and vascular fragility were observed frequently in JHS patients.

The light blue color of the sclera is due to the transparency of this membrane caused by the lack of collagen, transmitting the choroids plexus color. All different intensities have the same value when using this feature in the diagnosis of JHS and VEDS, but a very marked blue sclera should prompt consideration of the diagnosis of OI. Blue sclera was useful in the diagnosis of JHS in our subjects (Tables 2, 3, and 4). With experience, we have been able to distinguish 3 grades of blue sclera intensity: light (+), moderate (++), and marked (+++) (Figure 1). Blue sclerae were more frequent and more intense in female subjects (Tables 3 and 4). It is no surprise that 43% of the control subjects had blue sclera, considering that 39% of the controls had JHS. What is noticeable is the high frequency of blue sclera in the JHS patients (97%; $P < 0.05$ compared with controls), as seen in Tables 2 and 3. Since we did not use an objective study of blue sclera in the present study, we need to be cautious with our conclusions. It is most likely that the presence of blue sclera is an important sign, but reliability studies are needed to confirm this. For future studies, we are planning to use the universal color scale called Pantones colors, which uses codes for shades of different colors established by worldwide consensus.

Table 4. Comparison of blue sclera color intensity according to sex in patients with joint hypermobility syndrome*

Blue sclera	Men (n = 45)	Women (n = 162)
Negative	5 (11)	2 (1)
Positive		
Mild (+)	27 (60)	43 (27)
Moderate (++)	13 (29)	102 (63)
Marked (+++)	0	15 (9)

* Values are the number (%) of subjects. Note that the distribution of men and women was different ($P < 0.006$).

With regard to severe complications in the patients, it is interesting to note that none of the 230 JHS patients had cerebral aneurysm or uterine rupture, and only 2 JHS patients (0.9%) had spontaneous pneumothorax. This complication was more frequent in VEDS patients (11%). Consistent with previous descriptions of VEDS as having a more serious prognosis than JHS, we found that cerebral aneurysm (6%) and gravid uterus rupture (12%) were seen in VEDS patients, but none of the JHS patients developed these complications.

The typical facial appearance of JHS, as shown in Figure 2A, was useful in making the diagnosis. With practice and careful observation, we can recognize these patients by their facial appearance. The most striking characteristics are blue sclera and the cartilage changes in the ears and nose. The way they hold their head with extreme flexion of the MCP joints and wrists or with hyperextension of the fingers helps in the diagnosis of JHS (Figure 2B). The asthenic and marfanoid habitus features that are evident in some of the patients also help in the consideration of JHS as a possible diagnosis, particularly if the subject has back pain, scoliosis,

pectus excavatum, prominent lower ribs, or lumbar hyperlordosis.

In conclusion, we have shown that JHS, a forme fruste of the classic hereditary CTD, is a very frequent rheumatic condition that usually goes undiagnosed. The JHS typical facial appearance and the hand holding the head sign are helpful in considering the diagnosis of JHS. We have shown that it is possible to distinguish different degrees of blue sclera. The absence of arthralgias does not rule out the diagnosis of JHS or VEDS, since they were absent in half of the patients. The presence of JHS does not exclude the possibility of an associated arthritis. Dysautonomia, early osteopenia, and osteoporosis are frequently seen, both in JHS and in VEDS, and usually go undiagnosed in young patients. We recommend that these features be considered in the evaluation. We suggest that the presence of Raynaud's phenomenon in JHS should indicate the need to rule out an associated arthritis or cryoglobulinemia. Further studies are necessary to evaluate the frequency of dyslipidemia, acrocianosis, vascular fragility, xerophthalmia, and xerostomia, which were frequently seen in JHS. Severe complications can occur more frequently in patients with VEDS as compared with patients with JHS, including spontaneous pneumothorax, cerebral aneurysm, and gravid uterus rupture. Spontaneous pneumothorax can also be seen in JHS.

Finally, we agree with the findings in the literature that some JHS patients do not have hypermobility and yet still fulfill the Brighton criteria for JHS, and that the Beighton score alone is inadequate for the diagnosis of JHS. Further research is needed to better differentiate FM from JHS. We recommend that a validated hypermobility criteria set (i.e., the Brighton criteria or the Hospital del Mar criteria) be routinely used in the evaluation of rheumatology patients. Further studies are needed to determine why JHS is so frequent in Chile.

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