‘The hypermobility syndrome’

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The hypermobility syndrome is characterised by the occurrence of musculoskeletal symptoms in hypermobile subjects in the absence of demonstrable systemic rheumatological disease. When the syndrome was originally described in 19671 many rheumatologists viewed it with some scepticism—more as a clinical curiosity than a rheumatic disease. For one thing doctors and others are trained to examine for reduction of joint mobility rather than for an increased range, so that hypermobility is commonly missed. Secondly, the absence of laboratory abnormalities robbed the condition of scientific plausibility. Thirdly, there were no agreed criteria for hypermobility, merely a rather crude set of diagnostic manoeuvres, which have come to be known as the Beighton criteria.2 It is very much to its credit that despite criticism over the years, and despite various attempts to develop more sophisticated devices, the nine point scale has withstood the test of time and remains the universally adopted yardstick for clinical and epidemiological studies.

To what extent has our knowledge and understanding of this condition advanced over the past 22 years? The encouragingly large number of scientific contributions published from many countries and ranging over clinical, epidemiological, and basic scientific aspects attest to the substantial progress made in the understanding of this group of disorders.

Generalised ligamentous laxity, the prerequisite of joint hypermobility, is seen in a substantial proportion of healthy individuals (varying according to methodology and to the age, sex, and ethnic origin of the population studied), the overwhelming majority of whom probably suffer no ill effects. On the contrary, many derive added advantage in their pursuit of such activities as athletics, acrobatics, and ballet dancing, where greater flexibility is an asset.

Mobility for a given joint follows a Gaussian distribution,4 and within a population it is generally those subjects whose joint range is more than two standard deviations above the mean who suffer musculoskeletal symptoms.5 Hypermobility diminishes markedly throughout childhood and then more slowly during adult life. Women generally show a greater joint range than men, and Asians a greater range than Negroes, who in turn are more mobile than Caucasians. A recently established fact is that ‘pauciarticular hypermobility’ is even more prevalent in otherwise healthy subjects than the generalised variety. Among 660 North American music students of all ages 47% of the men and 78% of the women showed at least one hypermobile joint.

Generalised joint laxity is a feature common to a wide variety of heritable disorders of connective tissue, many of which are rare. By contrast the hypermobility syndrome, as seen in clinical practice, is a common finding. A diagnostic survey of 9275 new referrals to one large general rheumatology clinic showed that the syndrome was diagnosed more often than ankylosing spondylitis, crystal synovitis, or psoriatic arthritis, comprising 3·25% of all female and 0·63% of all male referrals.7 These patients present with a wide variety of readily identifiable traumatic and overuse lesions, such as traction injuries at tendon or ligament insertions, joint or tendon sheath synovitis, chondromalacia patellae, rotator cuff lesions, or back pain due to soft tissue injury or disc prolapse. Others suffer the effects of joint instability, such as flat feet, recurrent dislocation, or subluxation—notably of the shoulder patella, metacarpophalangeal joints, or temporomandibular joints. Others still, develop a chronic arthritis—either a low grade inflammatory synovitis of traumatic origin (which may mimic and consequently be misdiagnosed as rheumatoid or juvenile chronic arthritis) or osteoarthritis, which is held by many authorities (albeit on circumstantial evidence) to be a direct complication of the hypermobility syndrome.8 What sets the patient with the hypermobility syndrome apart from other rheumatology clinic attenders is the profusion and spectrum of common lesions occurring in the same individual and often spanning his (or more commonly her) whole lifetime.9 More difficult to explain in such patients is the commonly encountered arthralgia or myalgia in the absence of any demonstrable clinical abnormality. One postulated mechanism is the overstimulation of nociceptive nerve endings, which are poorly supported by defective collagen fibrils.10

Evidence has emerged from many centres that extra-articular organs and tissues, which rely for their structural integrity on the tensile strength of normal collagen, may also become disordered in hypermobile subjects. The skin may be thin, soft, hyperextensible, and develop striae. Fifty eight per cent of patients in one series showed such skin changes, and a characteristic facies has been described.10 An association between mitral valve prolapse and the hypermobility syndrome (and vice versa) has been reported in studies in the United Kingdom11 and in Czechoslovakia,12 and an increase in aortic compliance has been recorded.13 Weakness of the musculotendinous supporting structures of the anterior abdominal wall and pelvic floor no doubt explains the
reported increased finding of abdominal hernia, and of both rectal and uterine prolapse in subjects with hypermobility syndrome. Bone fragility may also be present, resulting in an increased liability to fracture. Stress fractures of the metatarsal bones and of the vertebral bodies and parts interarticularis of the lumbar spine are particularly common, the latter constituting additional potential sources of low back pain in the hypermobility syndrome. Another manifestation of bone softening seen in the syndrome is idiopathic protrusio acetabulæ. An additional feature, the marfanoid habitus, has also been described in patients with the hypermobility syndrome. In one series 39% were found to have a marfanoid habitus (defined as an upper segment:lower segment ratio of <0:89) compared with 11.5% of controls (p<0.05).

It was this constellation of clinical abnormalities observed in hypermobile subjects that gave rise to the hypothesis that the hypermobility syndrome was a forme fruste of a heritable disorder of connective tissue—a (mercyifully) benign overlap syndrome which incorporated many of the features seen in the rarer classical hereditary disorders such as the Marfan syndrome, the Ehlers-Danlos syndrome, and osteogenesis imperfecta.

A panel of 21 expert geneticists from 10 countries has recently drawn up an agreed comprehensive classification of the many syndromes and variants of syndromes that have been published ("The Berlin nosology"). Unfortunately, the patients with hypermobility syndrome described above as commonly displaying overlap features (marfanoid habitus, mitral valve prolapse, skin hyperextensibility, and joint laxity) do not fit comfortably into the Berlin nosology. Neither of the two nearest designations, the Ehlers-Danlos syndrome III (hypermobile type) and the familial articular hypermobility syndrome, are appropriate for this group. The skin and joint changes seen in the former are more florid, whereas in the latter syndrome skin involvement and mitral valve prolapse are reportedly absent. One hopes that this discrepancy will be considered in future revisions of the classification.

The multisystem pattern of the clinical features seen in the hypermobility syndrome points to a widespread disorder of connective tissue. As the increased fragility of the tissues concerned results from a loss of tensile strength it is reasonable to assume that it is the collagen which is at fault. Such evidence as is available lends support to this assertion. The question is—what defect(s)?

Skin biopsy samples showed raised ratios of collagen type III:types III+I in 14 out of 22 subjects with hypermobility syndrome, indicating a significant imbalance in the two major collagen types present. Electron microscopic examination of the same samples showed abnormally small collagen fibrils with an increase in interfibrillar matrix, elastin, and fibrilloses.

Studies of family pedigrees have provided evidence for a dominant mode of inheritance with sex-influenced phenotypic manifestations in most cases of the hypermobility syndrome. Within individual families women are more commonly and more severely affected than men, with a different phenotype pattern. Women tend to present with arthralgia and mitral valve prolapse, whereas men tend to develop dislocations, back pain, or torn menisci or tendons.

Although there have been recent exciting discoveries using molecular genetic techniques in many disorders, including variants of osteogenesis imperfecta and the Ehlers-Danlos syndrome, the application of such techniques to unravelling the mysteries of the hypermobility syndrome is still in its infancy. Preliminary work in selected families with hypermobility syndrome using the technique of segregation analysis suggests that the syndrome is not caused by a mutation involving collagen types I or III, nor the α-2 chain of type V or the α-3 chain of type VI (Brotherton, Child, Grahame, Henney, unpublished data).