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The real connective tissue diseases

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Rheumatologists and immunologists, in particular, are familiar with the connective tissues as a battlefield for a wide variety of inflammatory diseases, many of which are covered in this issue. The heritable disorders of connective tissue constitute a second, less familiar group which in recent years has yielded many of its mysteries to the techniques of molecular biology. Classification and accurate diagnosis of these conditions, affecting a wide variety of mesenchymal tissues, have benefited significantly from advances in basic science. A brief review is able only to scratch the surface of this fascinating group of conditions which have been extensively reviewed elsewhere[1,2]. Examples of disorders affecting the hard and soft musculoskeletal system will be used to illustrate general points.

Skeletal dysplasias

Skeletal dysplasias may be divided into those that affect bone (eg osteogenesis imperfecta) or the cartilage component of the bones (chondrodysplasias)[3]. The latter can be separated into those predominantly affecting the epiphyses or the metaphyses. Together with the presence or absence of spinal involvement, these simple descriptions form the basis of a clinical classification system:

- epiphyseal dysplasia
- metaphyseal dysplasia
- spondyloepiphyseal dysplasias, etc.

The presence of skeletal disproportion and its distribution can be useful clinically, for example:

- rhizomelic short limbs in achondroplasia
- relatively short trunk in spondyloepiphyseal dysplasia.

Several distinct families can be recognised within the skeletal dysplasias based on the underlying genetic abnormalities. The first to be well studied was osteogenesis imperfecta in which the diversity of clinical phenotypes correlates well with the mutations involving Type I collagen. Briefly, substitutions of cysteine for glycine in the critical central core of the collagen triple helix significantly impair formation of the classic triple helix of α chains, and lead to overmodification of the mature collagen by excessive glycosylation and hydroxylation. This type of mutation ('dominant negative') may reduce the amount of normal collagen by 7/8ths and lead to severe phenotypes (lethal or severely deforming). In contrast, mutations that create an effective null allele (eg premature stop codons) reduce the amount of normal collagen by smaller amounts and cause milder forms of disease. Similar attempts at classification based on the underlying biochemical and genetic defects have been possible in the chondrodysplasias (Table 1). The major cartilage collagen (more than 90%) is Type II. A large number of mutations have now been described in the gene *COL2A1*, identifying a family of chondrodysplasias[4]. These conditions are associated not only with abnormalities of the epiphyses but also frequently of the eye (Type II collagen is a major constituent of vitreous humour).

Soft connective tissues disorders

The heritable disorders of the soft connective tissues are best exemplified by the heterogeneous Ehlers-Danlos syndrome (EDS), characterised broadly by excessive skin elasticity, joint hypermobility and bruising, and the Marfan syndrome.

Ehlers-Danlos syndrome

Although 10 classic forms of EDS are described, many patients cannot be

Table 1. Examples of chondrodysplasias and the genetic loci involved.

Family	Member	Gene
Achondroplasia family	Achondroplasia	Fibroblast growth factor receptor-3 (*FGFR3*)
	Hypochondroplasia	
	Thanatophoric dwarfism	
Spondyloepiphyseal dysplasia	Achondrogenesis (Type II)	Type II collagen (*COL2A1*)
	SED congenita	
	Kneist dysplasia	
	Stickler syndrome	(some linked to *COL11A2*)
Multiple epiphyseal dysplasia	Pseudoachondroplasia	Cartilage oligomeric matrix protein (*COMP*)
	MED severe	Cartilage oligomeric matrix protein (*COMP*)
	MED mild	Type IX collagen (*COL9A2*)
Metaphyseal dysplasias	Type Schmid	Type X collagen (*COL10*)
	Type Jansen	Parathyroid hormone receptor-1 (*PTHR-1*)
Diastrophic dysplasia	Achondrogenesis-IB	Diastrophic dysplasia sulphate transporter
	Atelosteogenesis-II	
	Diastrophic dwarfism	
Craniofacial dysplasias	Apert syndrome	Fibroblast growth factor receptor-2 (*FGFR2*)
	Crouzon syndrome	
	Jackson-Weiss syndrome	

MED = multiple epiphyseal dysplasia; SED = spondyloepiphyseal dysplasia.

accurately categorised. The classic forms (Type I and II EDS) are caused by mutations in Type V collagen, a minor fibrillar collagen found in association with Type I collagen in the skin and blood vessels. The more severe acrogeric form (Type IV EDS), associated with rupture of hollow viscera and blood vessels, is deficient in Type III collagen due to a variety of mutations in *COL3A1*, the nature of which influences the severity of the phenotype. Type VII EDS, which presents with multiple joint dislocation, is caused by specific mutations in Type I collagen that lead to loss of the cleavage site for the N-terminal domain from the procollagen polypeptide. In this disorder of Type I collagen, it is of interest that osseous fragility is also seen.

Some of the features of EDS are shared with Marfan syndrome. Thus, benign joint hypermobility (Type III EDS) may be associated with some minor features (eg hypermobility, mitral valve prolapse), and lysyl hydroxylase deficiency (Type VI EDS), with tall stature, scoliosis, hypermobility and ocular fragility. Many other individuals in the community also exhibit minor degrees of soft tissue deficiency which defy formal classification. This may cause problems when trying to categorise patients accurately.

Marfan syndrome

Marfan syndrome is an autosomal dominant disorder with an estimated birth incidence of approximately one in 5,000, about 25% of the cases arising from new dominant mutations. Its clinical importance stems from the potential for catastrophic effects on the proximal cardiovascular tree. The multisystem nature of Marfan syndrome is due to defective fibrillin, a crucial component of microfibrils which are widely distributed in mesenchymal tissues, including the aorta, suspensory ligament of the lens, periosteum, skin and meninges.

Definitive diagnosis can be difficult

Table 2. Major criteria for the diagnosis of the Marfan syndrome.

Skeletal system (4 out of)	**Ocular system**
Pectus carinatum	Ectopia lentis
Severe pectus excavatum requiring surgery	
Disproportionate tall stature	**Cardiovascular system**
(upper segment:lower segment < 0.86 or span:height 1.05)	Dilatation of the ascending aorta
Wrist and thumb signs	Dissection of the ascending aorta
Scoliosis (>20º) or spondylolisthesis	
Loss of elbow extension (>10º)	**Dura**
Pes planus with valgus ankle	Lumbosacral dural ectasia
Protrusio acetabula	

Diagnosis requires two major criteria and involvement of a third system (eg mitral valve prolapse, striae or pneumothoraces). If a first-degree relative is unequivocally affected, only one major criterion and involvement of a second system is essential.

since the fully developed syndrome shares many features with other less severe clinical phenotypes carrying a much less adverse prognosis. A synopsis of the Ghent diagnostic criteria for Marfan syndrome is given in Table 2[5]. Wherever possible, a definitive diagnosis of Marfan syndrome or one of its related phenotypes should be made, rather than leaving the issue unresolved with a diagnosis of 'Marfanoid phenotype'. Individuals given such a diagnosis may conclude that they have Marfan syndrome and be faced with years of unnecessary anxiety if they in fact fit into one of the lesser phenotypes. All too commonly, patients referred with a putative diagnosis of Marfan syndrome have rather soft clinical signs such as tall stature, thin build, arachnodactyly, joint hypermobility and high arched palate, none of which constitutes a major criterion for the condition.

The differential diagnosis for Marfan syndrome is illustrated in Table 3. Of particular interest is the MASS phenotype, a condition characterised by the presence of minor features in several organ systems but excluding any major criteria for Marfan syndrome. These include myopia, mitral valve prolapse, mild aortic dilatation (less than two standard deviations above normal), skin features (eg striae) and skeletal involvement insufficient to constitute a major criterion.

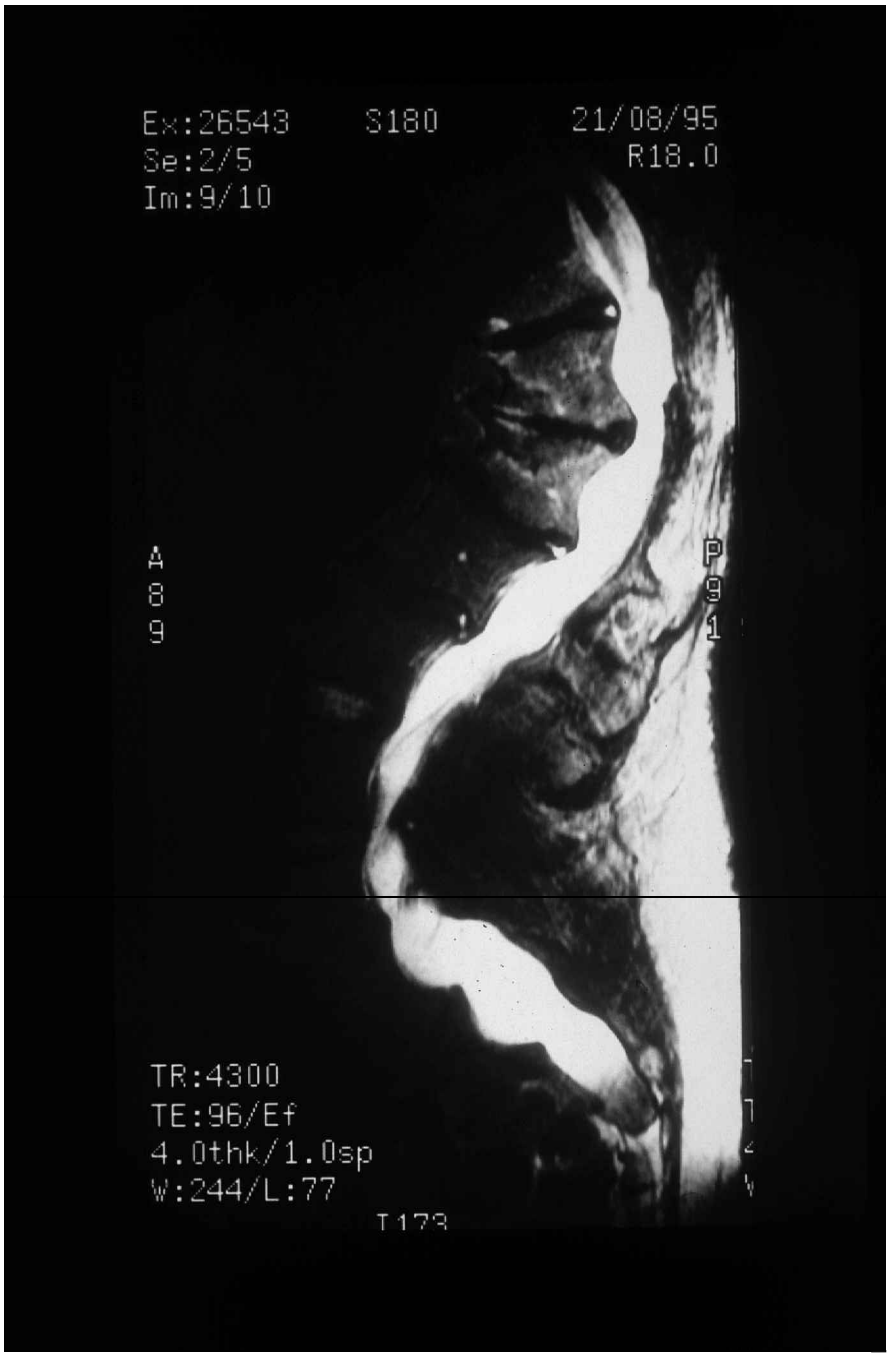
Familial Marfan-like habitus and familial ectopia lentis are distinguished by the presence of a major criterion in one organ system without major involvement of other tissues. Some of these patients will need occasional monitoring of the aortic root to be absolutely sure that signs do not develop late, but typically their prognosis is good. Familial aortic aneurysm or dissection obviously requires careful scrutiny.

Careful appraisal of the proximal cardiovascular tree is of crucial importance in the initial assessment of patients suspected of having Marfan syndrome. Echocardiographic evidence of significant or progressive enlargement of the proximal aorta is indicative of the more severe phenotypes, and should be sought in any individual satisfying major criteria

Table 3. The Marfan family.

- Marfan syndrome
- Familial Marfan-like habitus (<2 standard deviations above normal)
- Familial ectopia lentis
- Familial aortic aneurysm/dissection
- MASS phenotype (**m**yopia, **m**itral valve prolapse, **a**ortic root dilatation, **s**triae, **s**keletal involvement)
- Congenital contractural arachnodactyly (Beal syndrome linked to *FBN2* on chromosome 5)

Fig 1. Sagittal magnetic resonance image of lumbosacral spine demonstrating scalloping of the vertebrae by dural ectasia.



Key Points

- Numerous genetic causes for connective tissue diseases are now known
- Families of disorders can be recognised from the genes involved
- Not every tall person with arachnodactyly has Marfan syndrome
- Regular echocardiography should be undertaken in individuals suspected of having Marfan syndrome
- Lumbar magnetic resonance imaging may assist the diagnosis of Marfan syndrome

in other organ systems (ie skeleton, eye or dura). Magnetic resonance imaging of the lumbar spine looking for dural ectasia can help to establish a diagnosis of Marfan syndrome where definitive evidence from the classical systems is lacking (Fig 1). It is found in 60% of those with classic Marfan syndrome, but may also be present in individuals with less severe phenotypes. The severity of dural ectasia is highly variable, from modest effacement of the epidural fat through scalloping of the posterior border of the lumbar vertebrae to anterior meningocele. Mild variants of dural ectasia should be interpreted with care.

Management. Regular use of beta-blockers in patients with established Marfan syndrome and exhibiting evidence of aortic dilatation retards the progression of aortic distension, thereby delaying the onset of complications such as aortic dissection and aortic reflux. Serious consideration should be given to prophylactic aortic surgery in all individuals in whom the aortic diameter at the sinus of Valsalva reaches 5.5 cm. The use of beta-blockers and the introduction of elective surgery have probably significantly contributed to the increase in life expectancy that has recently been noted[6].

Screening

A variety of mutations in *FBN1* have been described in patients with Marfan syndrome[7]. These range from mutations causing premature stop codons (effectively null alleles) through mutations causing exons to be spliced out of the RNA transcript, to mutations likely to have profound structural effects on profibrillin (eg tyrosine for cysteine mutations ablating intra-chain disulphide bonds necessary for protein folding). Although genetic screening is practicable in many cases, it has not been our experience that it is widely sought by expectant parents.

Unfortunately, the wide range of mutations in the structural components found in these disorders of the mesenchymal tissues does not translate easily to potential cures.

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CME Septicaemia SAQs

Answers to CME SAQs published in *JRCPL* November/December 2000

Q1	Q2	Q3	Q4	Q5	Q11	Q12	Q13	Q14	Q15
a) T	a) F	a) T	a) F	a) F	a) T	a) T	a) T	a) F	a) T
b) T	b) F	b) F	b) F	b) T	b) F	b) F	b) F	b) F	b) F
c) T	c) T	c) T	c) T	c) F	c) F	c) T	c) T	c) T	c) T
d) F	d) T	d) T	d) F	d) F	d) T	d) F	d) F	d) T	d) F
e) T	e) T	e) F	e) F	e) T	e) F	e) F	e) F	e) F	e) F

Q6	Q7	Q8	Q9	Q10	Q16	Q17	Q18	Q19	Q20
a) F	a) T	a) F	a) F	a) F	a) T	a) T	a) T	a) T	a) T
b) T	b) T	b) T	b) T	b) F	b) T	b) T	b) T	b) F	b) T
c) T	c) F	c) T	c) F	c) T	c) T	c) F	c) T	c) F	c) T
d) F	d) F	d) F	d) T	d) T	d) F	d) F	d) T	d) F	d) F
e) F	e) T	e) T	e) T	e) T	e) T	e) T	e) T	e) T	e) F