Lessons from Marfan syndrome

Amongst the inherited abnormalities of connective tissue, Marfan syndrome continues to command particular attention, not least because of the realization that these individuals are best managed, long-term, in a specialist tertiary referral centre at which facilities for the monitoring of cardiac function and the size of the aortic diameter exist. Surgical repair is available if the aortic root widens to 5 cm diameter, preferably before it becomes torn and the risk to patients is reduced if blood pressure is monitored meticulously.

Nevertheless, there is still ample scope for diagnostic confusion. Although standard diagnostic criteria are published [1, 2], there is still substantial evidence of overlap between the different inherited abnormalities of connective tissue. It has been argued, persuasively, that the proband originally described by Marfan [3] in 1896 may actually have had a congenital contractural arachnodactyly. Attention has been drawn elsewhere to the overlap with Ehlers-Danlos syndrome and those felt to have ‘marfanoid Ehlers-Danlos syndrome’ [4] and even patients with benign joint familial hypermobility syndrome are frequently encountered with marfanoid habitus, although lacking the salient diagnostic pointers in the cardiovascular system and the eye. Many such patients seem to have blue sclerae, a feature recently suggested to be more common than expected in a population of hypermobile patients from Chile [5].

Although conventionally linked to a mutation in the gene for fibrillin-1 on chromosome 15 [6], this would seem not to be the whole story even when such testing is available. The number of possible identifiable mutations has increased over the decade; perhaps contributing to the observation that severity differs between individuals and within the same family. Either sex of any possible identifiable mutations has increased over the decade; perhaps contributing to the observation that severity differs between individuals and within the same family. Either sex of any ethnic group can be affected (the incidence is ~1:5000); 25% of all examples seeming to occur as the result of a spontaneous (new) mutation.

Against this background, this issue of Rheumatology contains a valiant attempt to measure muscle strength and body composition in a group of adult women with Marfan syndrome, showing that the reduction in muscle strength observed was not fully explained by a decrease in lean leg mass, and hinting at qualitative skeletal-muscle alterations related to abnormal fibrillin expression [7]. Clearly such studies are not easy. It would be unethical to select patients who were not already receiving protective beta-blockers, a group of drugs that can also influence muscle strength. Provision of a control group adequately matched in age to exclude a simple biomechanical cause of muscle weakness must have been difficult and the study does not address the, perhaps, remote possibility that the weakness might be as much neurological feature as a muscular one. Although discrete neuropathy is not recognized in Marfan syndrome, there has been much recent interest in abnormal proprioception in conditions associated with lax joints [8]. All those concerns raised, this still represents a useful study in an under-researched field.

Although clinical classification continues to be of interest, this has been overtaken in recent years by advances in fundamental research using Marfan syndrome as a model, which has led to a complete rethink on molecular pathogenesis. It has been known for about a decade that fibrillin-1 shares a high degree of homology with the latent transforming growth factor-beta (TGF-beta) binding proteins [9, 10]. TGF-beta cytokines are secreted as large latent complexes, which on secretion are sequestered by the extracellular matrix. This homology has prompted the hypothesis that extracellular microfibrils might participate in the regulation of TGF-beta activation. It is plausible that this might explain some clinical manifestations of Marfan syndrome such as the bone overgrowth and even changes in the heart valve since increased local activity of TGF-beta has recently been shown to be responsible for myxomatous cardiac valve disease in fibrillin-1 deficient mice [11]. Subsequently it was shown that mutations in the gene encoding the type II TGF-beta receptor exactly recapitulate the classic Marfan phenotype [12]. Although some individuals do not have all features of Marfan syndrome, it was subsequently shown that patients with Loey-Dietz aortic aneurysm syndrome, which has clinical features similar to Marfan syndrome, were heterozygous for loss of function mutations in either of the genes encoding the type I or type II TGF-beta receptor. The Loey-Dietz aortic aneurysm syndrome is also characterized by arterial tortuosity, diffuse aneurysm and dissections [13].

Conventional dogma on Marfan syndrome has taught that susceptible individuals are born with a structural weakness in the tissues, genetically determined with the consequence of tissue failure and fracture later in life. Previous management has been based on this conception. The new realization is that far from an all or nothing inherited condition, Marfan syndrome may well be post-natally acquired as a result of a failed regulatory (as opposed to a structural) role of the extracellular matrix. Suspicion points clearly to a deregulation of TGF-beta activity and signalling raising the prospect of prophylactic but not preventative intervention with cytokines. By implication, even if collagen is faulty in structure modification of the rate of production to produce greater quantities might protect from tissue damage later in life. The use of drugs that might modify TGF-beta activity suggests that phenotypes can be manipulated in the post-natal period in mice. That such manipulation might also be effective in man is not too distant a step. It even remains a possibility that such manipulation might not only benefit those diseases characterized by aortic dilatation and dissection but perhaps also those, such as the Ehlers-Danlos group, characterized by smaller aeurysm formation leading to cerebrovascular accident.

The ramifications of fibrillin-1 mutation may yet extend beyond clinics devoted to inherited abnormalities of connective tissue into those devoted to more inflammatory abnormalities of connective tissue. Increased TGF-beta signalling has been implicated not only in Marfan-associated mutant mice but also in fibrillin-1 deleted mice [14, 15]. Close homology between fibrillin-1 and fibrillin-2 [[16] may allow for compensation and a role for fibrillins has recently been suggested in dermal fibrosis based on work in Tsk (tight skin) mice [17]. This raises the possibility of an intriguing role for fibrillin in systemic sclerosis, possibly mediated by control of TGF-beta, normally accepted as the most probable mediator of fibrosis in this condition [18].

The putative potential for drugs, some already in development that might modify the regulation of cytokines in the TGF-beta super family is obvious. Although Marfan syndrome and systemic sclerosis might at first sight seem unlikely bedfellows, evidence for certain related pathogenetic features continues to accumulate, based upon the application of basic science to these diverse clinical conditions.
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References