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 contractual 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 ethnic group can be affected (the incidence is between individuals and within the same family. Either sex of any perhaps contributing to the observation that severity differs possible identifiable mutations has increased over the decade; Fahrbach et al. [6] have identified a fibrillin-1 mutation in an Ehlers–Danlos family and suggested an autosomal dominant transmission. 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-β1 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-β 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 Loeys–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-β receptor. The Loeys–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-β 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-β 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 only benefit those diseases characterized by aortic dilatation and dissection but perhaps also those, such as the Ehlers–Danlos group, characterized by smaller aneurysms 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-β 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-β, 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-β 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