The pathology of osteogenesis imperfecta

Osteogenesis imperfecta is a group of related, inherited disorders of connective tissues affecting approximately 1 in 30 000 of the population. The basic defect is abnormal synthesis of type I collagen molecules.

There are four main classes of osteogenesis imperfecta, designated I–IV with subclasses. Each class is named by reference to the genetic abnormality or clinical features, or both. Thus type I is known as dominant with blue sclerae; type II as lethal perinatal; type III as progressive deforming; and type IV as dominant with normal sclera.

As the names indicate, some forms of the disease are transmitted as autosomal dominant disorders, and by inference, others have autosomal recessive characteristics. The four classes encompass numerous gene defects caused by deletions, mutations, and insertions in the genes controlling formation of type I collagen.

Collagen is synthesised from three promolecules known as alpha chains. Within any type of collagen the chains may be all the same or different, but structurally related, molecules. The chains have designations such as alpha 1 (I) (the alpha 1 chain type I collagen). In the cell each alpha chain is altered, by cleavage, hydroxylation and glycosylation, before being combined with the other two to form a triple helix. The resultant molecule is known as procollagen.

The procollagen molecule is exported from the cell and, in the extracellular environment, the triple helix region is cleaved from its propeptides and assembled into collagen microfibrils. These then polymerise, often with other types of collagen, to form fibrils.

The genetic defects in osteogenesis imperfecta affect intracellular events in the process of synthesis and assembly of type I procollagen. Specifically, each subclass is characterised by abnormalities in the genes encoding the synthesis of the pro-alpha 1 (I) or pro-alpha 2 (I) chains, resulting in formation of (a) insufficient normal molecules; (b) unstable molecule; or (c) molecules that will not form helices. A transgenic model exists in mice in which a mutant gene for pro-alpha 1 (I) has been introduced into the mouse genome.

The most consistently described effect of abnormal type I collagen synthesis is a relative imbalance in the ratio of type I to type III collagen. Because of the way these two collagens are incorporated into the polymerised fibril, the most striking abnormality on ultrastructural examination of the tissue is a decrease in collagen fibre size.

Pathologically, the effects of these abnormal collagen fibrils are seen in those tissues which are particularly reliant on collagen fibre integrity for normal function. These include bone matrix, sclerae, dentine, tendons, blood vessels, and skin. Osteogenesis imperfecta usually presents with the consequence of poor bone formation and decreased bone mass, typically as vertebral and long bone fractures. In addition, the sclerae may appear blue because they are thinned and translucent, permitting partial visualisation of the underlying choroid; there are complex changes in tooth formation leading to small blue-yellow misshapen teeth; tendons and ligaments become lax, permitting an abnormal degree of joint movement; blood vessel walls become weakened; and the texture and resilience of skin becomes abnormal.

As its name suggests type II osteogenesis imperfecta has a very poor outlook. The altered collagen structure makes all the bones "brittle" and, as a consequence, the child is born with multiple fractures leading to trauma to the brain and poor ventilation.

Because it is a rare disease the pathological features of other forms of osteogenesis imperfecta tend to be reported anecdotally. In this issue of the Journal, McAllion and Paterson examine, for the first time, the causes of death in a sufficiently large series of patients with osteogenesis imperfecta to relate them to disease type.

It is well recognised that patients with type I osteogenesis imperfecta have a normal stature, but have an element of skeletal fragility, abnormalities of dentition, hearing impairment (due to compression of the eighth nerve by bony abnormalities), lax joints, and blue sclerae; class IV patients have similar, but less noticeable disorders. McAllion and Paterson have shown that despite the disease these patients have a normal life expectancy.

By contrast, the patients with type III osteogenesis imperfecta who, in life, have growth retardation, multiple fractures, progressive kyphoscoliosis, hearing impairment, and abnormal dentition, are at risk of dying prematurely from diseases secondary to their underlying collagen abnormality. This paper discusses the mechanism of death in these patients, but, in many ways it is what is not said that is as important as what is. The specific structural abnormalities in the type I collagen molecule in each subclass are known. McAllion and Paterson, by highlighting the mode of dying, identify a method in which the functional significance of specific parts of the collagen molecule can be related to the structural integrity of the tissue.

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Cytogenetics 40 years on

This year marks the 40th anniversary of Tjo and Levan’s historic observation that the correct diploid number of human chromosomes is 46.1 In common with comparable landmarks, their work represented the culmination of many scientific and technical developments permitting for the first time chromosome preparations of sufficient quality to identify correctly the human chromosome number. Their paper led to the advent of clinical cytogenetics, a genetic discipline which, over the past 40 years, has grown to provide the UK with a comprehensive, regionally based service.

Given the anniversary being celebrated this year, it is appropriate that this issue of the Journal should contain an article presenting the results of a survey which was designed primarily to discover the culture success rates and quality of the cytogenetic service currently being provided by 30 of the UK’s cytogenetic laboratories.2 As many of the clinicians referring tissue biopsy specimens from spontaneous abortions, fetal remains, stillbirths, and neonatal deaths for chromosome studies are pathologists, the results and recommendations of this study provide useful and practical guidelines on how to optimise the chance of successfully achieving a cytogenetic result from these specimens. One striking result was the high rate of maternal cell contamination following the culture of tissues derived from products of conception, the majority comprising early gestation spontaneous abortions. Although many couples who suffer early pregnancy loss may want to know whether a chromosome abnormality accounted for the miscarriage, the high rate of maternal cell contamination means that, in a high proportion of such specimens, the maternal karyotype is inadvertently examined. The most appropriate test, therefore, in couples with a history of recurrent miscarriages remains the examination of the parental chromosomes.

As cytogeneticists reflect on the first 40 years of their profession, it may be an appropriate time to determine how changes in the provision of cytogenetic services have evolved during this time and how they will develop in the next few years. The basic technical principles used by Tjo and Levan provide the foundation of many of the conventional cytogenetic techniques still widely used. However, cytogenetics has seen many scientific and technical advances over the past 40 years. Of these perhaps the most significant is the use of fluorescence in situ hybridisation (FISH) techniques, which is an approach to genetic diagnosis providing an essential bridge between genes and chromosomes. Most cytogenetic laboratories now routinely offer FISH for the diagnosis of a number of subtle chromosome abnormalities below the resolution of conventional microscopy—for example, microdeletion syndromes including DiGeorge and Williams.3 The growth over the past three years in FISH applications has been so rapid that in many centres between 10 and 20% of all postnatal cytogenetic samples now have one or more FISH tests carried out in order to diagnose or further elucidate a cytogenetic diagnosis.

Like so many innovative techniques, the growth in FISH applications will provide a number of challenges to cytogenetic laboratories throughout the western world. For example, trials are currently under way, most notably in America, to test the efficiency of using FISH with DNA probes in uncultured interphase nuclei as a way of detecting numerical abnormalities without having to examine the chromosomes. This approach, significantly faster than most conventional methods, can only be adopted after careful multicentre trials have been completed and validated but clearly may have a number of advantages, particularly in the field of cytogenetic prenatal diagnosis.4 One major disadvantage is that an invasive amniocentesis is still required in order to do the test. The American College of Medical Genetics issued a policy statement in 1993 warning against the overenthusiastic adoption of these new technologies and cautioning that all interphase diagnoses must be confirmed by conventional cytogenetics.5

The integration of FISH into cytogenetics not only provides a bridgehead between DNA and the chromosome, but underlines the growing tendency towards an integrated cytogenetic and molecular approach to the diagnosis of an increasing number of genetic conditions. The survey by Rodgers et al was commissioned by the Scientific Committee of the Association of Clinical Cytogeneticists, a professional body founded in 1976, who, in partnership with other professional groups including clinical geneticists, molecular geneticists and genetic nurses, joined forces in January 1996 to form the British Society for Human Genetics (BSHG).6 The formation of the BSHG is timely and will provide a much needed forum for increasing the scientific and professional integration of all doctors, nurses, scientists, and technologists currently providing genetic health care services in the UK.

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