NEWS AND COMMENTARY

Hereditary progeroid disorders and aging

Lessons from cutis laxa syndromes: wrinkles due to improper reloading of the extracellular matrix?

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Wrinkled and lax skin is an inevitable consequence of normal human aging. As resilience of the extracellular matrix is dependent on elastic fibres one obvious reason for reduced skin elasticity with increasing age is a degeneration of these fibres. As the expression of elastin is downregulated during postnatal development, elastic fibre damage accumulates with increasing age.¹ A part of this damage is ascribed to UV irradiation that promotes the formation of advanced glycation end products (AGE).² Ironically, recent results from an international study group on autosomal recessive cutis laxa (ARCL) found that impaired glycosylation in the Golgi apparatus also leads to wrinkled skin.³

In this issue Morava *et al* give an illuminating overview over the clinical and pathophysiological aspects of the different forms of ARCL. Although the patients often appear prematurely aged, the development of their skin phenotype is not simply an accelerated version of normal skin aging. For example, some individuals with ARCL type II (ARCL II) or wrinkly skin syndrome (WSS) are born with severe skin wrinkling that becomes milder with age. In gerodermia osteodysplastica (GO) skin wrinkling also is congenital but stays more or less constant until the normal aging process begins. In all forms of ARCL the dermal elastic fibres are improperly formed and scarce.⁴

However, as outlined in this article, the thinned, lax skin is the least important

clinical problem in this class of syndromal disorders. ARCL almost invariably is characterized by a generalized connective tissue weakness leading to hernias and joint dislocations. In most ARCL patients, osteopenia or even osteoporosis with increased fracture risk can be noted.⁵ Although some forms can lead to cardiovascular alterations and severe pulmonary disease, others often entail mental retardation with or without brain malformations that can have dramatic consequences.⁶ As cutis laxa disorders tend to overlap considerably differential diagnosis is a challenging task. As usual, the definitions of these rare disorders (about 200 families with ARCL have been reported worldwide) stem from a few first clinical descriptions. Depending on the precision of this first description more or less overlapping phenotypes were later lumped into the same entity. On the other hand, there are examples in which the same families were given different diagnoses by different clinicians.⁷ Due to this confusion several authors of cutis laxa case reports were unable to come to a clear diagnosis.^{8,9} As so often, this dilemma was overcome by a retrospective genetic analysis of patient cohorts that had been collected for decades. Although the resulting disease categories are sometimes not in complete agreement with the previously published ones it cannot be disputed that knowledge about the genetic defects in the different forms of

ARCL has made things easier. As pointed out by Morava *et al*, it should be noted that in a number of ARCL patients the genetic cause has not been identified which indicates further genetic heterogeneity.

Considering the progeroid aspect of many patients one obvious question is: do the ARCLs teach us something about normal human aging? As already indicated above, ARCLs are not progeria syndromes, which recapitulate human aging in a time lapse manner. But according to the definition given by George M Martin they can be regarded as segmental progeroid syndromes showing changes in some tissues that are reminiscent of aging.¹⁰ Therefore, the identification of the genetic causes of ARCL II/WSS and GO could help to broaden the scope of cellular processes that are believed to be involved in aging. The classical theories of human aging postulate that it mainly results from a combination of (1) an accumulation of mutations in the nuclear DNA due to defective repair mechanisms and (2) an increasing mitochondrial dysfunction that, among other effects, leads to elevated levels of reactive oxygen species.^{10,11} However, the defective gene products in ARCL II/WSS and GO, ATP6V0A2 and SCYL1BP1, respectively, reside in the Golgi compartment. Moreover, the loss of ATP6V0A2 function in ARCL II leads to a combined glycosylation defect demonstrating that impaired posttranslational modification can evoke progeroid changes.³ Although no generalized glycosylation defect has been detected in GO patients it cannot be excluded that there might be tissue-specific alterations that have escaped the standard diagnostic tools. Most of the changes that make us appear aged are based on an increasing rarefaction and rigidity of the extracellular matrix. Considering that the homeostasis of the extracellular matrix depends on highly active protein secretion and modification it is surprising that so few studies have investigated the connection between aging and changes in secretory pathway function. Further research on the genetic causes and pathomechanisms underlying hereditary segmental progeroid disorders with involvement of connective tissues such as ARCL might be able to define this connection in more detail ■

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