Journal of Cytology & Histology

Hassan et al., J Cytol Histol 2013, 4:1
DOI: 10.4172/2157-7099.1000166

Commentary Open Access

Clinical Outcomes of Elastin Fibre Defects

Ashfaq Ul Hassan[1]*, Ghulam Hassan[2], Zahida Rasool[3] and Shabinul Hassan[3]

[1]*Anatomy Department, SKIMS Medical College, Bemina, Srinagar, Kashmir, India*
[2]*Department of Anatomy, Al Qassim University, Saudi Arabia*
[3]*Islamic University of Science and Technology, Kashmir, India*

Abstract

Elastic fibres are a major class of extracellular matrix fibres that are abundant in dynamic connective tissues such as arteries, lungs, skin and ligaments. Their structural role is to endow tissues with elastic recoil and resilience. They also act as an important adhesion template for cells, and they regulate growth factor availability.

Mutations in major structural components of elastic fibres, especially elastin, fibrillins and fibulin-5, cause severe, often life-threatening, heritable connective tissue diseases such as Marfan syndrome, Menkes Syndrome, Cutis laxa. Elastic-fibre function is also frequently compromised in damaged or aged elastic tissues.

The ability to regenerate or engineer elastic fibres and tissues remains a significant challenge, requiring improved understanding of the molecular and cellular basis of elastic-fibre biology and pathology.

The aim of the article is to present in brief the structural details of elastin fibres, the defects and pleiotrophic effects as a result of damage and various clinical conditions associated with defects in elastin fibres ranging from rare pediatric syndromes to common entities like hypertension.

Keywords: Marfans syndrome (MFS); Menkes disease; Cutis laxa (CL); Fibrillin; Lysyl oxidase (LO); Homocystenemia

Introduction

Elastic fibers or yellow fibers are bundles of proteins (elastin) found in connective tissue and produced by fibroblasts and smooth muscle cells in arteries. Elastic fibers include elastin, elaunin and oxytalan. Elastic fibers stain well with aldehyde fuchsin, orcein, and Weigert's elastic stain in histological sections.

The permanganate-bisulfite-toluidine blue reaction is a highly selective and sensitive method for demonstrating elastic fibers under polarizing optics. Resilience and elastic recoil are properties conferred on all vertebrate elastic tissues by elastic fibers [1,2]. The amorphous component is made up of insoluble elastin, a highly cross-linked and hydrophobic protein assembled from soluble precursor proteins called "tropoelastins." The microfibrillar component of elastic fibers is composed of several glycoproteins, of which the best known are the fibrillins (fibrillin-1 and fibrillin-2). Once synthesized in early development, elastic fibers undergo very little turnover in normal adult tissues, with the notable exception of the uterus. The elastic fibers deposited in one's aorta as a young child, for example, are the same elastic fibers that one usually will die with. In a variety of elastic-tissue diseases, however, new elastic-fiber synthesis in adult tissue results in the aberrant accumulation of dysfunctional elastic fibers. Examples of such common disorders involving aberrant elastic-fiber assembly include emphysema, hypertension and aortic aneurysms. The various defects in the Expression, Structure, Assembly, Degradation of the constituent structural glycoprotein (or glycoproteins) of micro fibrils may be implicated in the causation of diseases associated with elastic fibres. It has been seen that a protein called fibulin-5, or DANCE (Developing Arteries and Neural Crest EGF-like) plays a substantial role in the generation and organization of elastic fibers in mice.

The mutations in fibrillin genes result in disorders affecting microfibril assembly are referred to as "fibrillinopathies." Although no mutations have yet been found in genes encoding other microfibrillar proteins such as MFAPs (Microfibril-Associated Proteins), it's entirely possible and indeed very likely that the fibrillinopathies will define a group of diseases due to mutations in several of the genes encoding microfibrillar proteins.

Elastinopathies are diseases due to mutations in the elastin gene. Together, both fibrillinopathies and elastinopathies can be considered as primary disorders of elastic fibers and as due to mutations in genes encoding proteins that are an integral part of elastic fibers.

Discussion

Marfan Syndrome (MFS) is a spectrum disorder caused by a heritable genetic defect of connective tissue that has an autosomal dominant mode of transmission. First described by the French physician Bernard JA Marfan in 1896, the defect has been isolated to the FBN1 gene on chromosome 15, which codes for the connective tissue protein fibrillin.1, Abnormalities in fibrillin protein cause a myriad of distinct clinical problems, of which the musculoskeletal, cardiac, and ocular system problems predominate. Connective tissue provides substance and support to tendons, ligaments, blood vessel walls, cartilage, heart valves and many other structures. In the Marfan syndrome, the chemical makeup of the connective tissue isn't normal. As a result, many of these structures aren't as stiff as they should be.

Marfan syndrome is caused by a fault in a gene on chromosome 15, which codes for the glycoprotein fibrillin. This is known as the fibrillin-1 gene or FBN1 for short. Fibrillin-1 is encoded by FBN1 on human chromosome 15q21 and fibrillin-2 is encoded by FBN2 on 5q23. Fibrillin is a major building-block of microfibrils, which

***Corresponding author:** Dr. Ashfaq Ul Hassan, MBBS, MS, Lecturer, Anatomy Department, SKIMS Medical College, Bemina, Srinagar, Kashmir, India, E-mail: ashhassan@rediffmail.com

Received December 03, 2012; **Accepted** January 30, 2013; **Published** February 01, 2013

Citation: Hassan AU, Hassan G, Rasool Z, Hassan S (2013) Clinical Outcomes of Elastin Fibre Defects. J Cytol Histol 4: 166. doi:10.4172/2157-7099.1000166

constitute the structural components of the suspensory ligament of the lens and serve as substrates for elastin in the aorta and other connective tissues throughout the body. Classical Marfan syndrome is associated with mutation in fibrillin-1, an important component of the elastic microfibril. Fibrillin-1 is a 350 kD glycoprotein, synthesized as a 375 kD precursor that is processed and secreted into the extracellular matrix (ECM). It polymerises to form microfibrils and helps to stabilize latent transforming growth factor -binding proteins (LTBPs) in the ECM. LTBPs hold Transforming Growth Factor-(TGF) in an inactive state. A failure of the interaction between fibrillin-1 and LTBPs may result in excess TGF signaling. Most fibrillin-1 mutations are missense, suggesting a dominant-negative effect on microfibrillar assembly. The defect renders the tissue compliant than it would be in a non-Marfan person. Since there is less tension at either end of the long bones, they keep growing while the individual does, becoming abnormally elongated. Weak connective tissue also explains the 'hypermobility of joints. Seen in Marfans syndrome is Synthesis of decreased amount of fibrillin

Synthesis and secretion of a normal amount of fibrillin but protein functions less efficiently than control cells.

Synthesis and secretion of normal amounts of fibrillin but the protein is poorly incorporated into extracellular matrix.

The most conspicuous ultrastructural defects were the

Formation of abrupt transverse tears in thick and compact elastic lamellae the local breaking up of smooth muscle cell–elastic lamella connections (that largely consist of microfibrils and elastic extensions, protruding from the elastic lamellae).

This breaking up was characterized by a strongly reduced number of microfibrils and a severe shortening of the elastic extensions.

Finally, the elastic extensions detached from the lamellae to ultimately degenerate and disappear [3].

Histopathological observations in heart also suggest the structure of all major components of connective tissue in floppy mitral valves is abnormal. Alterations in collagen and accumulations of proteoglycans are nonspecific changes that may be caused by the abnormal mechanical forces to which floppy mitral valves are subjected because of their excessively large surface area.

The presence of excessive amounts of proteoglycans may interfere with the normal assembly of collagen and elastic fibers. Abnormalities of elastic fibers resemble those in other conditions characterized by structural dilatation or tissue expansion and alterations in elastin could result from defective formation, increased degradation, or both.

The cardiovascular system in Marfans syndrome shows aortic dilatation, aortic regurgitation, and aneurysms as the most worrisome clinical findings. Mitral valve prolapse that requires valve replacement can occur as well.

Aortae from three patients with classic presentation of Marfan syndrome, who died of vascular complications, were subjected to biochemical analyses of the connective tissue. A corresponding increase in lysyl residues was noted in elastin II preparations. Also, the concentration of elastin per milligram dry weight of tissue was reduced in Marfan cases. It was also seen that cross-linking of aortic elastin is reduced. Thus, a defect in elastin could explain the vascular fragility observed clinically in these patients [4].

Ocular findings include myopia, cataracts, retinal detachment, and superior dislocation of the lens.

The skeleton of patients with MFS typically displays multiple deformities including arachnodactyly (i.e, abnormally long and thin digits), dolichostenomelia (i.e, long limbs relative to trunk length), pectus deformities (i.e, pectus excavatum and pectus carinatum), and thoracolumbar scoliosis.

Cutis Laxa (CL) comprises a rare and heterogeneous group of disorders characterized by lax inelastic skin with or without internal manifestations. The skin of CL patients tends to hang in loose folds, giving an appearance of premature ageing. In contrast to Ehlers–Danlos syndrome, the skin in CL is neither hyperelastic nor fragile; wound healing is normal and there is no joint hypermobility.

Gastrointestinal tract: Diverticula of the small and large bowels may be present; rectal prolapse may occur.

Pulmonary: Bronchiectasis, emphysema, and cor pulmonale may be present. In acquired CL, pulmonary involvement typically manifests as emphysema due to the loss of the elastin support network and is the most common cause of death in these patients.

Cardiovascular: Cardiomegaly, congestive heart failure, murmurs, cor pulmonale, and aortic aneurysms may occur. Severe aortic disease may be present as a result of aortic vessel medial degeneration and extracellular elastin deposits lacking microfibrillar elements.

Skeletal: Dislocation of the hips; osteoporosis; and other skeletal abnormalities, such as growth retardation, delayed fontanelle closure, and ligamentous laxity, may be present. In several cases, skin fibroblast tropoelastin production is markedly reduced

Histological evaluation of aortic aneurysmal specimens indicated classical hallmarks of medial degeneration, paucity of elastic fibres, and an absence of inflammatory or atherosclerotic lesions. Electron microscopy showed extracellular elastin deposits lacking microfibrillar elements. Direct sequencing detected defects in exon 30 of the elastin gene in affected individuals. The histopathologic analysis of the skin in affected cases reveals Alterations in the quantity alterations in the the morphology of elastin in which fragmentation or a loss of elastic fibers is present. Additionally, evidence of abnormal cross-linking of elastin exists in some patients with CL. Cultured dermal fibroblasts from patients with CL have shown increased elastolytic activity compared with healthy skin, and elastolysis has been suggested to result from increased elastase activity.

No specific histologic abnormality is seen on routine stains with hematoxylin and eosin. On elastic fiber stains, all types of CL show a reduction in the number of elastic fibers throughout the dermis, with remaining fibers being shortened, clumped, granular, or fragmented.

In severe cases, no elastic fibers may be present, but only fine, dustlike particles scattered throughout the dermis can be seen. In cases preceded by an inflammatory eruption, such as urticaria or vesicles, the inflammatory infiltrate may be mononuclear (lymphocytes and histiocytes) or mixed, containing neutrophils. Electron microscopic examination reveals degenerative changes in the elastic fibers, which are variable from case to case. However, the most significant finding is the presence of electron-dense amorphous or granular aggregates that are irregularly distributed in the vicinity of the elastic fibers.

Menkes disease also known as kinky hair disease is an X-linked neurodegenerative disease of impaired copper transport. Menkes et

al. first described it in 1962 [5]. Danks noted that copper metabolism is abnormal in 1972; after noting the similarity of kinky hair to the brittle wool of Australian sheep raised in areas with copper-deficient soil, he demonstrated abnormal levels of copper and ceruloplasmin in these patients. In Menkes disease, transport of dietary copper from intestinal cells is impaired, leading to the low serum copper levels. Abnormal copper transport in other cells leads to paradoxical copper accumulation in duodenal cells, kidney, pancreas, skeletal muscle, and placenta.

Hair changes: Abnormal kinky hair, eyebrows, and eyelashes. Often lightly or abnormally pigmented; can be white, silver, or gray. In ethnic groups with black hair, the hair can also be blonde or brown. Associated are abnormal facies, Progressive cerebral degeneration, and Connective-tissue abnormalities. Loose skin at the nape of the neck and over the trunk.

Joint hyper mobility, Polypoid masses, which can be multiple, in the gastrointestinal tract, Umbilical and inguinal hernias, which can be bilateral, Bladder diverticula, Dilated ureters, Emphysema, Arterial rupture Brachial, lumbar, and iliac artery aneurysms, Internal jugular vein aneurysms.

Menkes' kinky hair syndrome is associated with the defecive functioning of several copper-dependent enzymes due to impaired copper absorption, transport, or metabolism. Lysyl oxidase is a copper-requiring enzyme that catalyzes the oxidative deamination of lysyl residues linking two adjacent chains of tropoelastin polypeptides into an insoluble network, Elastin of the connective tissue is the responsible protein for the elastic properties of the skin [6].

Decreased Lysyl Oxidase (LO) activity accounts for the connective-tissue fragility and vascular abnormalities in Menkes disease, since LO deaminates lysine and hydroxylysine in the first step for collagen cross-linkage. LO localizes to the trans-Golgi network so subcutaneous injections of copper-histidine do not improve the activity of LO as the copper is not delivered into the Golgi apparatus.

Hypertension and some congenital heart defects are associated with alterations in the great arteries, arteries, and arterioles with alterations in the elastic matrix. Research suggests that any factor that reduces elastin during a critical window of vessel wall formation and alters large artery compliance could have a modifying effect on the progression of, or susceptibility to, hypertension. As elastin is the dominant extracellular protein in large arteries, the effects of elastin defect on these vessels is to be expected [7].

Homocystenemia in humans is associated with vascular complications that increase the risk for atherosclerosis and stroke. Animal studies have shown that the disease is multifactorial and includes lesions associated with the elastin component of the extracellular matrix.

References

1. Cleary EG, Gibson MA (1996) Elastic tissue elastin and elastin associated microfibrils. In: Comper WD Extracellular matrix Harwood. Amsterdam 95–140.
2. Debelle L, Tamburro AM (1999) Elastin: molecular description and function. Int J Biochem Cell Biol 31: 261–272.
3. Dingemans KP, Teeling P, van der Wal AC, Becker AE (2006) Ultrastructural pathology of aortic dissections in patients with Marfan syndrome: Comparison with dissections in patients without Marfan syndrome. Cardiovasc Pathol 15: 203-212.
4. Abraham PA, Perejda AJ, Carnes WH, Uitto J (1982) Marfan syndrome. Demonstration of abnormal elastin in aorta. J Clin Invest 70: 1245-1252.
5. Menkes JH, Alter M, Steigleder GK, Weakley DR, Sung JH (1962) A sex-linked recessive disorder with retardation of growth, peculiar hair, and focal cerebral and cerebellar degeneration. Pediatrics 29: 764–779.
6. Martins C, Gonçalves C, Moreno A, Gonçalves O, Baptista AP, et al. (1997) Menkes' kinky hair syndrome: ultrastructural cutaneous alterations of the elastic fibers. Pediatr Dermatol 14: 347-350.
7. Martyn CN, Greenwald SE (1997) Impaired synthesis of elastin in walls of aorta and large conduit arteries during early development as an initiating event in pathogenesis of systemic hypertension. Lancet 350: 953-955.