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Pseudoxanthoma Elasticum: Genetics, Clinical Manifestations and Therapeutic Approaches

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Abstract. Pseudoxanthoma elasticum (PXE) is an inherited disorder that is associated with accumulation of mineralized and fragmented elastic fibers in the skin, vascular walls, and Bruch's membrane in the eye. Clinically, patients exhibit characteristic lesions of the posterior segment of the eye including peau d'orange, angioid streaks, and choroidal neovascularisations, of the skin including soft, ivory-colored papules in a reticular pattern that predominantly affect the neck and large flexor surfaces, and of the cardiovascular system with peripheral and coronary arterial occlusive disease as well as gastrointestinal bleedings. There is yet no definitive therapy. Recent studies suggest that PXE is inherited almost exclusively as an autosomal recessive trait. Its prevalence has been estimated to be 1:25,000–100,000. Very recently, the ABCC6 gene on chromosome 16p13.1 was found to be associated with the disease. Mutations within ABCC6 cause reduced or absent transmembraneous transport that leads to accumulation of extracellular material. Presumably, this mechanism causes calcification of elastic fibers. Despite the characteristic clinical features, the variability in phenotypic expressions, and the low prevalence may be responsible for the disease being underdiagnosed. This review compiles and summarizes current knowledge of PXE pathogenesis and clinical findings. Furthermore, different therapeutic strategies to treat retinal manifestations are discussed, including thermal laser coagulation, photodynamic therapy, and intravitreal injections of drugs inhibiting vascular endothelial growth factor. (**Surv Ophthalmol** 54:272–285, 2009.

Key words. ABCC6 • angioid streaks • anti-VEGF • cardiovascular system • choroidal neovascularisation • genetics • peau d'orange • pseudoxanthoma elasticum (PXE) • skin

Historical Background

The French dermatologist Rigal described skin changes characteristic for pseudoxanthoma elasticum (PXE) initially in 1881,[102] followed by the histologic examination of the skin changes by his collegue Balzer. As both did not realize the implications of their findings, the term *pseudoxanthoma elasticum* was coined in 1896 by another

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French dermatologist—Ferdinand-Jean Darier,[27] who aimed to differentiate the newly described diseases from the common xanthoma (yellow papule) of the skin. Angioid streaks were first described by the English ophthalmologist Doyne in 1889 and the German ophthalmologist Plange in 1891, with the German-born American ophthalmologist Hermann Knapp introducing the term *angioid streaks* to the scientific community in 1892.[63] According to Knapp's theory, angioid streaks were due to hemorrhages at the posterior pole leading to dark brown or black pigmented streaks. In 1929, two Swedish physicians, the ophthalmologist Ester Gröenblad and the dermatologist James Strandberg, for the first time realized the association between angioid streaks and PXE and termed the syndrome *Groenblad-Strandberg* syndrome.[47] Since then Groenblad-Strandberg syndrome and pseudoxanthoma elasticum are used synonymously.

Epidemiology

PXE has been described worldwide. The exact prevalence is unknown, with a recent estimated range between 1:25,000 and 1:100,000.[21] Prevalence seems to be higher in South Africa compared to other regions, possibly due to a founder effect.[28] Applying the Hardy-Weinberg equilibrium, this leads to a frequency of 1.25% heterozygotes (1:80).[21] In 2002, a prevalence of 3% of heterozygous carriers of the R1141X mutation of the *ABCC6* gene was reported in a Dutch population of young patients affected by coronary heart disease. However, the prevalence of this mutation among healthy controls was 0.76%.[125] This high prevalence was unexpected and would lead to an estimated prevalence of heterozygous carriers of about 3% as it constitutes about one-fourth of mutant alleles in the investigated population.[21] However, these results stand to be replicated in other countries. It is unknown whether the classic PXE-phenotype represents only a small proportion of ABCC6-mutation carriers.[21] Women seem to be affected twice as often as men, and life expectancy is normal in most patients.[21]

Pathophysiology

The rate of synthesis as well as degradation of elastin has been found to be increased in skin specimens of PXE patients.[6,90,126] Baccarani-Contri and coworkers were able to document the process of calcification and subsequent fragmentation of elastic fibers. Using immune electron microscopy, an increased protein biosynthesis, for example, of vitronectin as well as an accumulation of abnormal matrix proteins with a high affinity to calcium and calcifying compounds, has been demonstrated.[10] Quaglino and coworkers used cutaneous fibroblasts to demonstrate altered cell–cell and cell–matrix interaction and a disturbed glycosaminoglycan metabolism.[98] The changes in glycosaminoglycan metabolism are reflected by increased enzyme activity of xylosyltransferase I in serum specimens of PXE patients.[42] Xylosyltransferase I is the initial enzyme in the biosynthesis of glycosaminoglycans and already has been identified as a serum marker for increased proteoglycan biosynthesis.[44] Against this background, fibroblasts have been investigated extensively regarding their role in the pathogenesis of PXE. However, the identification of the *ABCC6* gene raises the question of a connection between an altered transmembrane transporter in the liver and kidneys and the mineralization of elastic fibres in other organ systems. Taking this into consideration, PXE could represent a metabolic disorder due to a decreased or absent function of the ABCC6 gene product that remains to be identified.[127]

Interestingly, hereditary hemoglobinopathies such as beta-thalassemia cause similar ultra-structural changes of the skin, eyes, and cardiovascular system without *ABCC6* mutations.[3,50] This suggests alternative pathologic mechanisms such as increased levels of chronic oxidative stress, which indeed could be demonstrated in fibroblasts of PXE patients, are involved.[89] For a more extensive review of the histopathology and pathophysiology of PXE, the reader is referred to Hu and co-workers.[56]

Genetics

PXE was first described to be a sporadic disease, followed by reports of autosomal dominant and recessive inheritance.[97] Current evidence points toward an autosomal recessive inheritance. No pedigree with three affected generations has yet been described,[21] and autosomal recessive and dominant forms alike have been localized on chromosome 16p13.1.[121] The same *ABCC6*-mutations have been described in families with assumed recessive and dominant inheritance.[12] Pseudo-dominance has been described in two families.[103] Should there be autosomal dominant patterns of inheritance in PXE, their role may be marginal.[96]

Assuming a solely autosomal recessive inheritance, unaffected parents of affected children have a 25% chance of bearing another affected child. However, no prediction about the phenotype can be made. The risk for PXE patients to give birth