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Case Report

Pseudoxanthoma Elasticum

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Abstract

Groenblad-Strandberg syndrome, also known as Pseudoxanthoma Elasticum (PXE), is a rare heritable disease. The skin, retina, and cardiovascular system are frequently affected by this genetic connective tissue disease. Discrete lesions usually first appear on the skin, then extra-dermal symptoms appear. The diagnosis is influenced by clinical symptoms, histological analysis of the lesions, and genetic testing. It is also known as multisystem orphan illness. Mutations in the ABCC6 gene cause Pseudoxanthoma Elasticum (PXE), a genetic metabolic disorder with an autosomal recessive inheritance pattern. Ectopic mineralization, which is most easily seen inside the elastic tissues of the skin, eyes, and blood vessels, is brought on by the absence of the beneficial ABCC6 protein. The ATP-dependent transmembrane transporter family member ABCC6 (also known as MRP6), whose gene codes for the protein, is expressed largely in the liver and kidneys and only slightly less in organs that are affected by PXE. Lack of functional ABCC6 protein results in ectopic mineralization, which is especially noticeable in the elastic tissues of the skin, eyes, and blood vessels. In 1881, French dermatologist Rigal became the first person to describe the condition in writing. Even though the physiological substrates of ABCC6 are still unclear, the current theory is that PXE should be viewed as a metabolic disorder with unknown circulating chemicals interfering with the synthesis, turnover, or maintenance of elastic fibres. The degree of extracutaneous organ involvement determines the Pseudoxanthoma Elasticum prognosis (PXE).

Keywords: Mineralization, Elastic fibres, Heterogenous, Ectopic, Calcification, Cutaneous

Epidemiology

Pseudoxanthoma Elasticum (PXE) is a rare heritable condition with a higher prevalence in women and an estimated prevalence of 1 per 100,000 to 1 per 25,000 in the general population. Clinical symptoms are rarely visible at birth and typically appear in the second or third decade of life. Many siblings in PXE families are impacted. Precise estimations cannot be supported since variables are more expressive [1,2].

Genetics

One of the rare ectopic mineralization syndromes, PXE, is autosomal dominant or recessive with complete penetrance and is brought on by homogenous or heterogenous mutations in the ABCC6 gene on chromosome 16p13.1. Since there is currently no molecular proof of autosomal dominant inheritance, the persistence of PXE across many generations may be explained by a pseudo-dominant pedigree pattern caused by familial consanguinity. A significant number of incidents also happen sporadically. Remarkably, genetic mutations in the SPP1 gene's promoter (also known as osteopontin) may be a hereditary risk factor for PXE susceptibility [3]. The pathologic mineralization process in PXE may also be influenced by dietary factors, such as consuming many dairy products during puberty or infancy or absorbing aluminium hydroxide, a phosphate binder. Even though its specific substrate is still unknown, a recent study shows that ABCC6 functions as a transmembrane transporter of polyanionic glutathione-conjugated molecules. The ABCC6 gene transporter protein also referred to as multidrug resistance-associated protein 6 (MRP6), is a member of the adenosine triphosphate-binding cassette proteins primarily expressed in the liver and only weakly in the proximal tubules of the kidney and intestine. It is the source of the pathogenic inactivating mutations that cause the usual type of PXE, which affects 90% of patients. PXE patients have been associated with over 300 mutations in the ABCC6 gene, including intronic alterations, small deletions and insertions, missense, and nonsense mutations. The most frequent loss-of-function mutations are p.R1141X and g.del23-29, which make up much to 45% of all pathogenic PXE mutations. In 5% of PXE patients, disease-causing mutations of the ENPP1 gene, which codes for Ectonucleotide

Pyrophosphatase/Phosphodiesterase 1, are present. The gradual mineralization and disintegration of elastic fibres is the histology characteristic of PXE [3].

Pathophysiology and Histology

Although the genetic nature of the condition is widely established, little is understood about the pathophysiological process of PXE. Even though ABCC6 is necessary to release ATP from the liver, it has been suggested that ABCC6 does not carry ATP. Although the liver, kidneys, and intestines are where ABCC6 is most prominently expressed in healthy people, the damage in PXE patients is more pronounced in these remote regions. There are essentially two hypotheses that might be true. First, the cell-based explanation states that peripheral areas deficient in functional ABCC6 protein lead to ectopic mineralization. The cell-based theory is called into question by the discovery that, in healthy controls, ABCC6 mRNA is expressed only at low to moderate levels in tissues other than the liver, although cultured fibroblasts derived from PXE patients' dermis exhibit biochemical and genetic abnormalities [4]. Generalized Arterial Calcification of Infancy (GACI) is a deadly autosomal recessive disorder marked by widespread arterial calcification that first manifests in the first few months of life [3,4]. The ENPP1 gene's inactivating mutations are associated with decreased levels of inorganic pyrophosphate, a potent physiological inhibitor of the development of hydroxyapatite crystals and extracellular matrix calcification. Interestingly, some GACI patients have described PXE-like cutaneous symptoms. Additionally, fetuin-A, a crucial negative regulator of mineralization, had decreased levels in the serum of PXE patients, indicating that fetuin-A may be a part of the etiology of PXE. The slow mineralization and breakdown of elastic fibres, which produce the histological imaging pattern known as elastorrhexis, is the primary histological hallmark of PXE. These alterations can be observed by utilising Light Microscopy (LM) and Electron Microscopy (EM) in other tissues containing elastin and in the principal organs of PXE patients that are injured, such as the skin, retina, and blood vessels [5].

Skin, the retina, and blood vessels-all of which include elastin-are the organs most commonly affected by the changes detected on Light Microscopy (LM) and Electron Microscopy (EM) in each of the organs above. Aneurysm formation is caused by the internal and external elastic laminae of blood vessels fragmenting and intimal thickening, which increases the risk of rupture. Over time, Bruch's membrane, located in the retina between the retina and choroid, becomes harder. The tiny, yellow papules, which no longer have their regular interlacing pattern, have altered the skin architecture [5,6].

Discussion

Rigal, a French dermatologist, first identified the condition in 1881. Ferdinand-Jean Darier developed the term pseudoxanthoma elasticum in 1896 to distinguish it from xanthomas. Consequently, Robert W. Doyne and Otto Pflange described pseudoxanthoma Angioid streaks in the retina for the first time in 1889 and 1892, respectively. Two Swedish physicians, dermatologist James Strandberg and ophthalmologist Ester Gröenblad, first identified the connection between angioid streaks and Pseudoxanthoma Elasticum (PXE) in 1929. The skin, eyes, and cardiovascular system are the primary organs of the uncommon inherited illness PXE. Elastic fibre degeneration and aberrant connective tissue mineralization are its defining traits. A common symptom of the disorder is skin symptoms, which account for most PXE cases and are frequently the first apparent indicators of the disease as it advances. Small, yellowish papules that grow into plaques are distinctive cutaneous features, and they usually develop on the sides of the neck and resemble "gooseflesh" or "plucked chicken skin." The groin, perineum, periumbilical area, axillae, and thigh are ideal locations. Usually discovered in the second or third decade, these skin lesions. The damaged skin is loose and hangs in apparent folds in older people [7,8]. Even though they are not pathognomonic, angioid streaks, which are brought on by the rupture of elastic laminae in the Bruch membrane of the retina, are the hallmark eye symptoms of PXE. They are irregular reddish-brown or grey streaks that come from the optic disc. With an average onset age of between 15 and 25 years, they appear to be present in at least 85% of PXE patients. Although angioid streaks are initially asymptomatic, they subsequently progress to become the sites of choroidal neovascularization and subretinal haemorrhages, which can impair central vision in cases of macular involvement [6].

In general, all primary and medium-sized arteries are impacted. Chronic calcification of elastic arterial walls causes the development of cardiovascular disease symptoms. Haemorrhages are caused by a highly fragile vessel wall, whereas a reduction in the vessel lumen causes ischemia. Clinically, the most common cardiovascular symptom and typically the first sign of accelerated atherosclerosis is intermittent claudication, which affects 30% of patients. Coronary artery disease and renovascular hypertension, which can cause angina pectoris, myocardial infarction, congestive cardiac failure, renal failure, and stroke, are more likely to develop in younger PXE patients. Although PXE patients typically lead everyday lives, the degree of system involvement affects morbidity and mortality. The affected people are more likely to experience ischemic heart disease, strokes, eyesight loss, and skin ageing. When compared to the population, life expectancy is lower. Identifying illnesses as soon as possible is essential to lessen the chance of systemic effects. You are highly encouraged to live a preventative lifestyle, visit the doctor frequently, and get genetic counselling [6,9]. There is no standard course of treatment for PXE. When the appearance of the skin lesion presents a cosmetic problem, plastic surgical excision has been used successfully. Neovascularization and retinal haemorrhages can be stopped with laser photocoagulation. Aspirin, non-steroidal anti-inflammatory drugs, and other platelet inhibitors like warfarin should generally be avoided if you want to reduce your risk of bleeding.

Symptoms and Diagnosis

PXE often starts in infancy or adolescence and initially affects the skin. One of the findings is the distribution of whitish papules between 1 and 5 mm along the lateral neck and flexural areas. There

may also be reticular or linearly clustered lesions that can damage the vaginal, oral, or rectal mucosa. The lesions become more extensive and resemble "cobblestones" over time. Over time, the damaged skin becomes supple, malleable, and somewhat wrinkled. There is substantial mental (chin) folding in asymptomatic lesions. [9] All PXE patients have bilateral ocular anomalies, which first manifest in early adolescence or childhood. Initial lesions are asymptomatic, but as people age, they may develop into vision loss. "Orange skin" or "pea d 'orange" refers to the speckled appearance of the temporal retina. Thin, erratic stripes called angioid streaks look like blood vessels. Regions of chorioretinal atrophy at the retina's periphery are known as comet tails. A pathognomonic trait of PXE is these. As a result of Bruch's membrane breaks, a process known as choroidal neovascularization occurs in which subretinal arteries develop (CNV). This profound side effect manifests as the sickness gets worse and vision deteriorates [5,6]. Characteristics of the heart include disease of the peripheral arteries. Aneurysms, transient ischemic attacks, and "Carotid stenosis," a later-stage form of coronary artery disease, can cause angina and myocardial infarction. Strokes (7-15%). On rare occasions, PXE patients may encounter the following systemic symptoms: Symptomatic calcification of the renal arteries, reduced pulmonary function, benign calcification of the breast, pancreas, testicles, spleen, and liver, and urinary or gastrointestinal bleeding (15%). Chest pain, vision loss, and ischemic or hemorrhagic strokes are the side effects of pseudoxanthoma elasticum, severe sudden limb claudication bleeding in the GI tract, early on in a pregnancy, and miscarriage is more frequent [10]. Pregnancy nearly always causes stretch marks, commonly known as striae. Elastosis perforans serpiginosa is a skin disorder that several illnesses, including PXE, can bring [7,6].

The characteristic skin changes that PXE generates can be used to diagnose it; histological confirmation is frequently useful. Ophthalmologists may do a fundoscopy to diagnose pathognomonic ocular features. Histopathology research may be used to pinpoint PXE. Various staining methods can reveal calcium deposits, shorter and cracked elastic fibres, and collagen fibre deformation. Genetic testing for ABCC6 mutation homozygosity or compound heterozygosity is the standard gold test for PXE. More than 90% of patients exhibit mutations. Additionally, genetic testing can rule out conditions that mirror PXE [3].

Differential Diagnosis

a) Solar elastosis

b) Perforating calcific elastosis

c) Chronic D-penicillamine use

d) Linear focal elastosis

e) Mid-dermal elastolysis

f) Cutis laxa

Management and Treatment

Even though some patients' treatment for the disease's nuchal and axillary symptoms may be motivated by cosmetic considerations, surgery for these non-life-threatening symptoms should be performed in prudence. One patient has impromptu tried antioxidant therapy with daily doses of tocopherol acetate and ascorbic acid because of the theory that oxidative stress leads to PXE. After 12 months, the skin lesions had returned, but at 18 months, they had started to advance. Additionally, the delivery of an antioxidant meal had little impact on mineralization in the Abcc6/ mouse model [3]. Vascular endothelial growth factor (VEGF) inhibitor intravitreal therapy has quickly gained popularity as a successful treatment for reducing choroidal neovascularization, typically the most significant symptom of PXE. Thus, the use of physical treatments like photodynamic therapy has decreased. Contact sports should be avoided because retinal haemorrhage is potential. The current strategy for treating the cardiovascular symptoms of PXE involves altering one's lifestyle to lower cardiovascular risk factors (smoking cessation, weight loss, daily walking, moderate physical exercise, etc.). According to studies on the drug's administration in this disease, a third of 1,747 PXE patients were using or had previously taken cholesterol-lowering medicines, according to an analysis of the effects of atorvastatin administration in a murine model of PXE. Because damaged retinal neovasculature increases the risk of bleeding, acetylsalicylic acid is typically contraindicated in PXE [5-10]. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and antiplatelet medications should be avoided, especially in cases of gastrointestinal bleeding. However, this risk must be weighed against the advantages of thrombophilia prophylaxis.

Researchers have studied the effects of dietary supplements in both animal models and humans to understand the potential pathophysiological theories for PXE (including possible circulating pro- or anti-mineralization agents). The Abcc6 (/) mice showed improvements in several illness indicators after taking magnesium supplements. It is unknown if a low-calcium diet would be practical during infancy to reduce ectopic mineralization, even though a high calcium intake during infancy has been associated with the severity of PXE [3]. PXE is a promising candidate for gene therapy. Given that mutant ABCC6 heterozygotes show few if any, PXE features, the presence of a single healthy allele or modest expression should be enough to relieve disease symptoms. The liver expresses ABCC6 the highest, making it logical to target a transgene to this organ. New delivery strategies and technological advancements are being developed for liver-directed gene therapy. Plasmid-based gene therapy has been assessed using the Abcc6 / murine PXE model.

Siblings have a 25% chance of developing PXE due to its Mendelian autosomal recessive inheritance. There is no reason to advise against getting pregnant despite placental calcification and low birth weight because neither the mother's nor the fetus's odds of conception are increased. Children born to a PXE patient, and a non-affected individual will not be affected by inheritance, except endogamy and genetic isolates where pseudodominance has been demonstrated [6-3].

Conclusion

PXE is currently recognized as an ectopic mineralization-related autosomal recessive metabolic, genetic disease that affects the skin, eyes, and blood vessels. Although PXE does not pose a

life-threatening concern, it has been linked to peripheral artery dysfunction, an increased chance of going blind, and a worse standard of living. PXE has no recognized treatment; thus, persons who have it need to be closely watched (clinical examinations, exploration of the vascular tree with MR angiography and ultrasound, fundus examination of the posterior pole of both eyes). Moderate exercise and avoiding eye damage are two behavioural and lifestyle considerations. Plastic surgery could be an option if skin manifestations negatively impact the quality of life. Before doing vascular surgery, a few procedures must be completed. Given that PPi is believed to act as the circulating anti-mineralization factor, it should be possible to create and verify disease-modifying treatments. However, the specific pathophysiological mechanisms behind the metabolic state are yet unknown.

Acknowledgments

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Conflict of Interest

None.

References

1. Barbara Marconi, Ivan Bobyr, Anna Campanati, Elisa Molinelli, Veronica Consales, et al. (2015) Pseudoxanthoma elasticum and skin: Clinical manifestations, histopathology, pathomechanism, perspectives of treatment. Intractable Rare Dis Res 4(3): 113-122.
2. Jouni Uitto, Qiujie Jiang, András Váradi, Lionel G Bercovitch, Sharon F Terry (2014) Pseudoxanthoma Elasticum: Diagnostic Features, Classification, And Treatment Options. Expert Opin Orphan Drugs 2(6): 567-577.
3. Dominique P Germain (2017) Pseudoxanthoma elasticum. Orphanet Journal of Rare Diseases 12: 85.
4. N Chassaing, L Martin, P Calvas, M Le Bert, A Hovnanian (2005) Pseudoxanthoma elasticum: a clinical, pathophysiological and genetic update including 11 novel ABCC6 mutations 42(12): 881-892.
5. Catarina Lucas, João Aranha, Isabel da Rocha, Domingos Sousa (2020) Case Report: Pseudoxanthoma elasticum [version 1; peer review: 1 approved, 3 approved with reservations]. F1000Res 9: 9.
6. Sheila Z Jalalat (2022) Pseudoxanthoma Elasticum. Dermatology.
7. D Marco L, Lima Martínez M, Karohl C, Chacín, Bermúdez V (2020) Pseudoxanthoma Elasticum: An Interesting Model to Evaluate Chronic Kidney Disease-Like Vascular Damage without Renal Disease. Kidney Dis 6(2): 92-97.
8. Francesco DL, Dario PM, Vittoria M, Laura P, Daniela Q, et al. (2021) From Clinical Diagnosis to the Discovery of Multigene Rare Sequence Variants in Pseudoxanthoma elasticum: A Case Report. Front Med (Lausanne) 8: 726856.
9. Mohammad J Hosen, Anouck Lamoen, Anne D Paepe, Olivier M Vanakker (2012) Histopathology of pseudoxanthoma elasticum and related disorders: histological hallmarks and diagnostic clues. Scientifica (Cairo) 2012: 598262.
10. Yasir Al Dojaily, Darshan Singh (2001) Pseudoxanthoma elasticum. DermNet.