The Libyan International Medical University

Faculty of Basic Medical Science

How Psesudoxanthoma Elasticum affects the eye.

Sudad Eltalhi.

Supervised by: Dr. Khadija Mansur.

Assisted by: Dr. Mohamd Haj.

Report Submitted to fulfill the requirements for Scientific Research Activity

Date of Submission: 16/2/ 2019

Abstract:

The term Pseudoxanthoma Elasticum (PXE) was coined by the French dermatologist Ferdinand-Jean, due to its characteristic yellow tone of skin, it is a genetically determined autosomal recessive disorder involving the ABCC6 gene, the lack of functioning ABCC6 protein is mostly prominent on the elastic tissues, effecting their structure and thus and leaving them in a state of fragmented, loose elastic tissue, seen as small yellow papules on the nap and sides of neck, the skin becoming wrinkled and loose, and the elastic fibers are fragmented, usually involves various organs including the skin, eyes, cardiovascular system, and gastrointestinal tract, the clinical prevalence of Pseudoxanthoma Elasticum has been estimated at between 1 per 100,000 with slight preference to females, making Pseudoxanthoma Elasticum extremely rare, unfortunately there is no cure for this condition.

Introduction:

Pseudoxanthoma Elasticum is a rare genetic autosomal recessive disorder, caused by a mutation in the ABCC6 gene, the lack of functional ABCC6 protein leads to ectopic mineralization of abnormal accumulation of calcium/phosphate deposits, in which the dystrophic calcification most apparent in the elastic tissue, (calcification of the elastic fiber, specifically effecting the skin, eyes, blood vessels, cardiovascular system, gastrointestinal system) [(1)]. The condition is characterised by loose connective tissue, distributed yellowish papules involving the neck, axillia, umbilicus, and groin, sometimes the mucus mucosa is involved, and the skin becomes loose and wrinkled, result of the shortened, fragmented, calcified elastic fibres[(2)]. When Pseudaxanthoma Elasticum affects the eyes the changes usually appear years after the skin changes, as Angoid streaks, a result of breaks in the elastic Bruch membrane of the Retina and may result in severe injury of eye (in worst case it results in blindness)[(2)] . In the following discussion it will be shown how the genetic mutation in ABCC6 will affect the elastic tissue.

Methods and materials:

As this is literature report, the only material available is hypothetical theories and multiple scientific studies.

Discussion:

Pseudoxanthoma Elasticum is a rare genetic disorder, it is autosomal recessive inheritance, with a slight preference to females is seen, as they are affected nearly twice as often as males, the reason of preference is still not known, these mutations effect the skin first and then may cause ocular change without systemic manifestations, PXE may present in disease such as sickle cell disease, thalassemia, and more rarely Ehlers Donals Syndrome[3].

Most patients have been noted to have inherited sporadic mutations, giving that there are about forty three mutations of the ABCC6 gene of the chromosome 16p13. Therefore the lack of functioning ABCC6 proteins (effecting the adenosine triphosphate binding cassette proteins (ATP), which are involved in signal transcription, protein secretions, drug and antibiotic resistance,) most evidence suggest PXE as a metabolic disease in which the levels of the anti-metabolite inorganic pyrophosphate (PPi) are low, a result the lack of ATP release, leading to ectopic mineralization of the elastic tissue that is most apparent in the skin, blood vessels, and eyes, eaving the tissue worn, fragmented, and calcified [4].

Patients with Pseudoxanthoma Elasticum first clinical sign are presented with small yellowish bumps called papules usually on the neck, the papules coalesce making the skin loose and wrinkled[1]. At least 10% of the diseased people will present with gastrointestinal hemorrhage, due to the gastrointestinal system tissue weakened structure [3].

These ophthalmological manifestations of Pseaudoxanthoma Elasticum are secondary but are the most dangerous, seeing as in later stages they can lead to blindness[3].

It has been noted that 87% of patients who suffer from Pseudoxanthoma Elasticum who suffer from associated Angioid streaks in the eye specifically in the Bruch membrane, the Angoid streaks are presented as progressive disorder that is characterized by the presence of the streaks in the eye, the streaks are variable in color (red/brown/grey) reflecting the

lesions in Bruchs membrane, a result of the accumulation of deposits of calcium (mostly) and other minerals in elastic fibers.

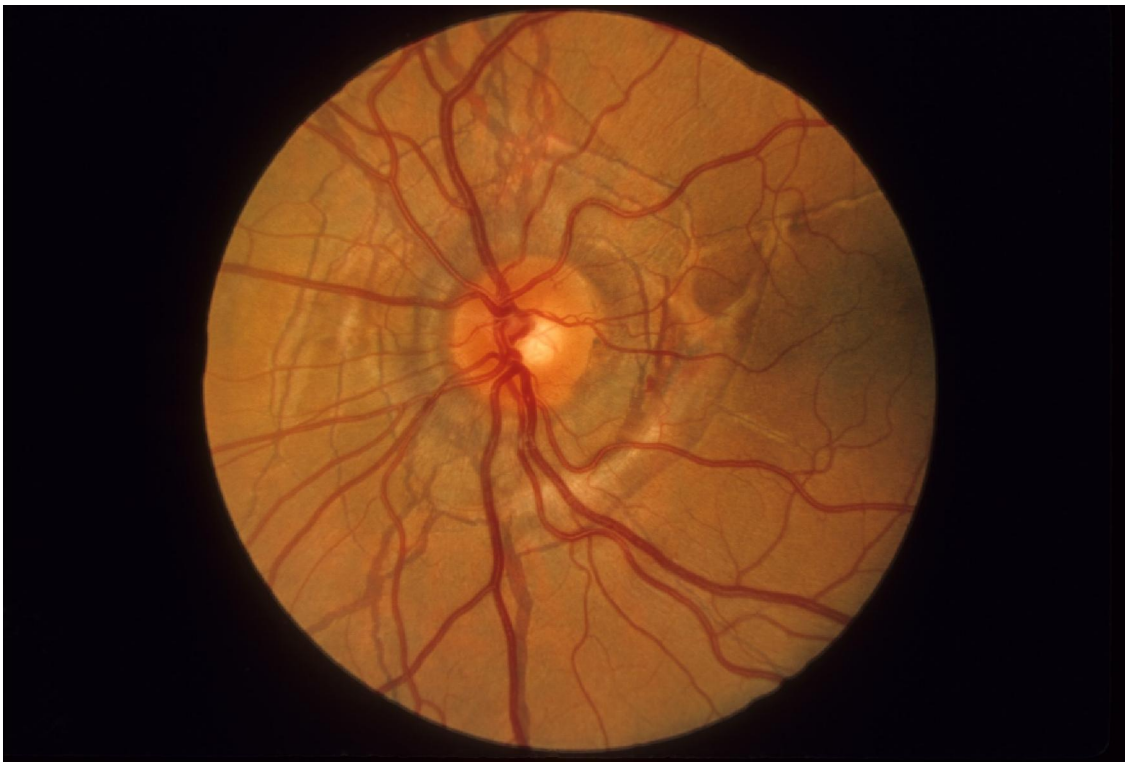
The bruch membrane is therefore seen as shortened, fragmented and calcified, elastic fibers in the membrane, they appear as bilateral cracks deep to the retinal vascular architecture and radiate from the optic nerve coursing in all directions [(2)].

The Angoid streaks decreases the strength and flexibility of structures throughout the eye, they may become symptomatic when reaching the fovea of the macula, but the Ophtalmopathies are not evident until later on in life, hemorrhage or occlusion often present afterwards giving Peau d'orange[(1)].

The Angiod streaks represent as a major threat to vision and as the disease progresses, the calcification of Bruchs membrane may trigger choroidal neovascularization, resulting in bleeding, furthermore forms scarring tissue and fibrosis, frequently involving the central macula, and ultimately loss of central vision if not treated, concluding that Angoid streaks are the cause of blindness[(4)], this does not affect the peripheral vision as it remains normal, this involvement mostly occurs at the fourth decade in life, and patients are visually handicapped by the age of fifty [(3)].

Another abnormality in the eye is Peau d'orange, (orange peel skin), the fundus may have areas of yellow molting temporal to the fovea, which is a change in the pigmented cells of the retina. Especially in those with early onset and rapid progression of disease [(3)].

A significant proportion of patients have atrophy of the retinal pigment epithelium, and outer retina [(3)].



(Figure 1) Charateristic ophthalmologic feature of pseaudoxanthoma elasticum: angiod streaks[4]

Lastly it has been speculated that long term treatment of D-penicillamine used to cure willions disease has been shown to cause Pseudoxanthoma Elasticum, the penicilliamine chelates copper and leads to its depletion, which is a cofactor in oxidase and is important in elastine cross linkage, penicilamine stops lysyl oxidase, inhibiting the synthesis of collagen and elastin fibers leading to Peasudoxanthoma Elasticum[5].

Conclution:

Pseudoxanthoma Elasticum is a well characterized, autosomal recessive, genetic disorder, although it is not a life threating disease it could cause blindness and decrease quality of life, there is no cure for this condition but patients should be monitored on a regular basis, patient should avoid trauma to the eye and try to include moderate exercise in their lifestyle, if quality of life is significantly impaired plastic surgery can be considered.

References:

1. Kuan-Jen Chen, Shira G. Ziegler, (2017) Ectopic calcification in Pseudoxanthoma Elasticum Responds to Inhibition of Tissue-Nonspecific Alkaline Phosphatase. Issue of JAMA Ophtalmology.
2. Kuan-Jen Chen MD, (March 1, 2017) Angioid Streaks and Other Retinopathy in Pseudoxanthoma Elasticum, Issue of JAMA Ophthalmology.
3. Sharon F Terry, MD (June 14, 2012). Ophthalmology Review Manual 2nd Edition | Cornea | Epithelium.
4. Georgalas I, Tservakis I, Papaconstaninou D, Kardara M, Koutsandrea C, (2010) Pseaudoxanthoma Elasticum, Ocular Manifistations, Complications and treatment. Clinical And Experimental Optometry, 94(2), 169-180.
5. Chisti MA, Binamer Y, (January, 2019). Penicillamine Induced Pseudoxanthoma Elasticum with Elastosis Perforans Serpiginosa.