

Pseudoxanthoma elasticum – Genetics, pathophysiology, and clinical presentation

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ARTICLE INFO

Keywords:

Pseudoxanthoma elasticum
PXE
Bruch's membrane
ABCC6

ABSTRACT

Pseudoxanthoma elasticum (PXE) is an autosomal-recessively inherited multisystem disease. Mutations in the *ABCC6*-gene are causative, coding for a transmembrane transporter mainly expressed in hepatocytes, which promotes the efflux of adenosine triphosphate (ATP). This results in low levels of plasma inorganic pyrophosphate (PPI), a critical anti-mineralization factor. The clinical phenotype of PXE is characterized by the effects of elastic fiber calcification in the skin, the cardiovascular system, and the eyes.

In the eyes, calcification of Bruch's membrane results in clinically visible lesions, including peau d'orange, angioid streaks, and comet tail lesions. Frequently, patients must be treated for secondary macular neovascularization.

No effective therapy is available for treating the cause of PXE, but several promising approaches are emerging. Finding appropriate outcome measures remains a significant challenge for clinical trials in this slowly progressive disease.

This review article provides an in-depth summary of the current understanding of PXE and its multi-systemic manifestations. The article offers a detailed overview of the ocular manifestations, including their morphological and functional consequences, as well as potential complications. Lastly, previous and future clinical trials of causative treatments for PXE are discussed.

1. Commercial relationship Disclosures

All authors: No commercial relations with any role in the design or interpretation of the information in the article.

2. Introduction

Pseudoxanthoma elasticum (PXE, Online Mendelian Inheritance in Man [OMIM] 264800) is an inherited systemic disease affecting mainly the skin, the cardiovascular system, and the eyes. Dermal alterations are

characterized by small yellowish papules, first appearing in the neck and intertriginous sites. Cardiovascular involvement includes premature atherosclerosis, especially of the femoral arteries, that is often partially compensated by extensive collaterals due to the slow progression of the disease. Ocular alterations are driven by the calcification of Bruch's membrane (BrM) (Gliem et al., 2013a; Marconi et al., 2015; Brampton et al., 2021); (Gliem et al., 2013a; Marconi et al., 2015; Brampton et al., 2021).

The calcification process in the eye starts around the optic nerve head and spreads towards the periphery throughout the patient's life.

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<https://doi.org/10.1016/j.preteyeres.2024.101274>

Received 4 February 2024; Received in revised form 17 May 2024; Accepted 20 May 2024

Available online 28 May 2024

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Funduscopically, this calcification is visible as a whitish area, compared to the red fundus appearance in uncalcified sites. The border between (peripheral) uncalcified BrM and (central) calcified BrM is called 'peau d'orange' and appears as a mottled brownish-white lesion. Within the calcified area, breaks of BrM are visible, called angioid streaks (AS) (Gliem et al., 2013a; Charbel Issa et al., 2010), AS are not pathognomonic for PXE, as they appear in other diseases with BrM alterations, such as sickle-cell and Paget's disease (Saito-Hakoda et al., 2023; Condon and Serjeant, 1976; Goldberg et al., 1971). Choroidal neovascularization (CNV) is frequent in PXE, often forming along AS and can be treated with intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections (Gliem et al., 2020a; Finger et al., 2011a). A causal therapy for PXE is still lacking, but several approaches targeting the lower levels of inorganic pyrophosphate (PPi, Fig. 1) in PXE are emerging (Jansen et al., 2014a). In this review, we summarize the current knowledge on PXE with a focus on ocular alterations and present current treatment approaches under investigation in pre-clinical development and clinical trials.

3. History and Terminology

3.1. Description of the skin disease

The name pseudoxanthoma elasticum for a distinct skin disease was first introduced by French dermatologist Ferdinand-Jean Darier in 1896 (Darier, 1896), but reports of putative PXE-like skin lesions were published before (Rigal, 1881; Balser, 1884).

3.2. Grönblad-Strandberg-syndrome

The Swedish ophthalmologist Ester Elisabeth Grönblad first reported the multi-systemic phenotype of PXE, noting the association of ocular findings (angioid streaks), inguinal and axillary skin changes, and cardiovascular disease. The diagnosis of PXE – until that time considered a skin disease – was made in these patients by the dermatologist James Victor Strandberg in 1929 (Grönblad, 1929; Strandberg, 1929). As her Ph.D. thesis, Ester Grönblad published the first comprehensive review on AS in PXE, including the ocular phenotype in 1932 (Grönblad, 1932)

and another case series on 41 patients in 1958 (Grönblad, 1958).

Notably, others have also reported an association between the ocular phenotype and unspecified skin alterations (Oeller, 1900) or even diagnosed PXE before (Hallopeau and Laffitte, 1903).

Following Grönblad and Strandberg's reports, the reported multi-systemic nature of the disease was swiftly confirmed by multiple investigators (Marchesani and Wirz, 1931; Poos, 1931; Lewis, 1933; Krantz, 1932).

3.3. Historical description of the ocular phenotype

The history of the first descriptions for most PXE-associated ophthalmic lesions is complex, as the same lesions were repeatedly reported as 'novel' findings with varying names. Although a monogenetic disease, the descriptions are still of value, as the diagnosis is given by the combination of clinical characteristics with a support by genetic variants.

3.4. Angioid Streaks

In 1889, Doyne first described 'irregular, jagged lines' in a patient with blunt trauma and the patient's fellow eye, already identifying the characteristic location around the optic disc (Doyne, 1889). An independent report on 'pigmented striae' was published by Plange in 1891 in the *Archives of Ophthalmology* (Plange, 1891). The editor J. Hermann Knapp attached to this publication one of his cases as a third case and introduced the term 'angioid streaks' (Knapp, 1892) due to the similarity to retinal vessels on funduscopy (Fig. 2).

More reports with larger case series were published soon. In 1927, Holloway reviewed the literature to date, including 58 reported cases, and added 2 own patients with AS from the literature by then (Holloway, 1927).

The correct histologic correspondence of the lesions was first suggested by Kofler and Lohmann (Kofler, 1917; Lohmann, 1923). First histologic studies supported this hypothesis about 20 years later (Hagedoorn, 1939; Böck, 1938).

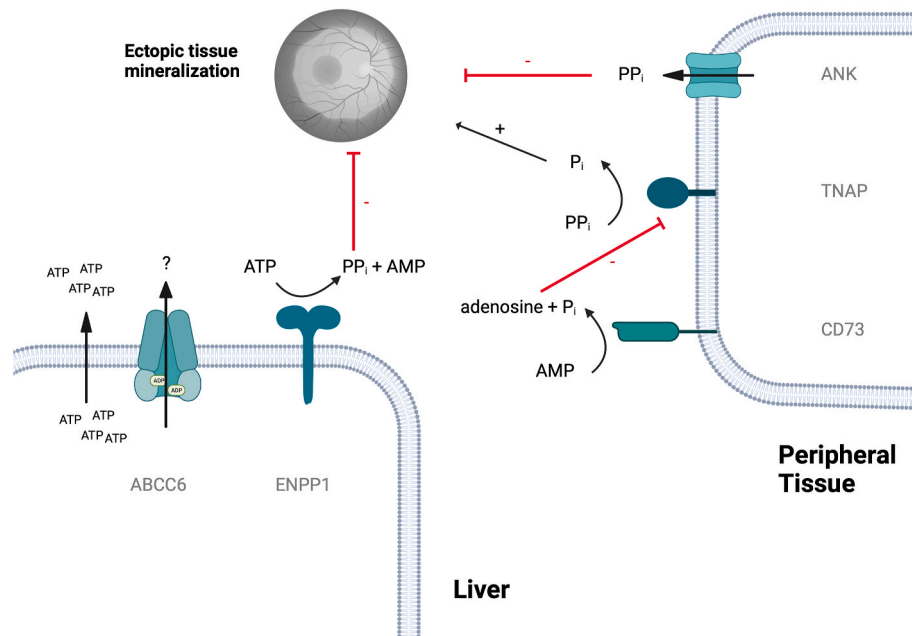


Fig. 1. Pyrophosphate pathway

Ectopic tissue mineralization in PXE is a complex process involving not only ABCC6, but also ENPP1, CD73 and TNAP. See Chapter 4 'Disease mechanism' for a detailed description.

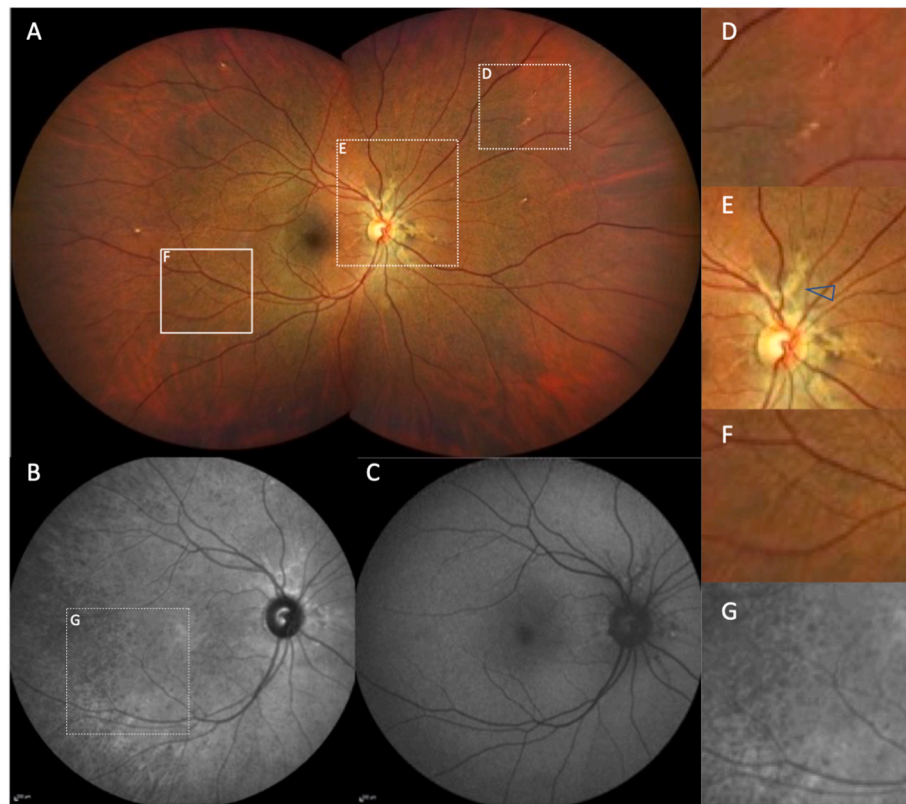


Fig. 2. Overview of ocular characteristics in Pseudoxanthoma elasticum

Fundus photography (A), infrared reflectance (IR-)imaging (B) and short-wavelength fundus autofluorescence (C) of an eye with PXE. In the mid-periphery, comet tail lesions (D) can be found. Their tail points towards the posterior pole. Around the optic disc, breaks in Bruch's membrane can be found (E, blue arrowhead), that radiate towards the periphery. The streaks never cross peau d'orange (F), which is the border of calcified and uncalcified Bruch's membrane. This transition zone is better visible in IR-imaging (G), where the mottled aspect in the central border (i.e., uncalcified BrM to transition zone) is best appreciable.

3.5. *Peau d'orange*

Already in her 1932 review, Grönblad noted that AS end in a region of 'grobe Körnelung' (German for 'coarse granulation') (Grönblad, 1932) and identified this lesion as the putative leading disease front. The term 'grobe Körnelung' was also used in the English literature (Grönblad, 1958).

It was also reported very early based on the examination of siblings, that this lesion precedes AS (Zeeman, 1933).

In 1964, Smith and coworkers re-described the same lesion using fluorescein angiography and named it *peau d'orange* (French for 'orange peel skin'), which is the most frequently used term today (Smith et al., 1964).

3.6. *Calcified Bruch's membrane*

Various terminologies have been introduced to describe the calcified BrM area. Initially, the area of calcified BrM was called 'graue Zone' (German for 'grey zone') (Grönblad, 1932) based on funduscopic observations. Later publications introduced terms such as area 2 (for the area of increased fundus reflectivity on infrared imaging, presumably resulting from BrM calcification) (Charbel Issa et al., 2010) or *Coquille d'œuf* (French for 'egg shell') on colour fundus photography to describe the same lesion (Spaide, 2015).

3.7. *Pattern dystrophy*

A mottled fundus appearance has been described as an auxiliary finding in Plange's and Knapp's descriptions of cases with AS (Plange, 1891; Knapp, 1892). In 1955, Bischler (BISCHLER, 1955) used the terms

'le fond d'oeil moucheté multicolore' (French for 'multicolored speckled eye fundus') and Shimizu (1961) 'mottled fundus' for describing PXE-typical pattern-dystrophy like changes. Also, the descriptive term fundus pulverulentus pattern-dystrophy has been used in the context of PXE (Agarwal et al., 2005).

3.8. *Comet tail lesions*

Donald Gass proposed the term 'comet tail lesions' in 2003 for the lesions appearing like punched-out areas in the mid-periphery (Gass, 2003a) (Fig. 2). To date, both comet lesions and comet tail lesions are established for describing these lesions with and without tails, respectively.

4. Epidemiology, inheritance and genetics

The prevalence of PXE has been estimated to be 1:56,000 (95%CI 1:35,000 to 1:97,000) based on a Dutch cohort but might be higher, as new mutations have been discovered not included in this analysis (Kranenburg et al., 2019). The disease is caused by bi-allelic mutations in the *ABCC6* gene with an autosomal-recessive pattern of inheritance (Le Saux et al., 2000; Bergen et al., 2000; Ringpfeil et al., 2000; Struk et al., 2000).

ABCC6 is located on chromosome 16 (16p13.1) and belongs to the subfamily C of ATP-binding cassette genes. This family codes for channels, mostly active pumps, while the actual substrate of this specific transporter is not yet identified (Bergen et al., 2000; Plomp et al., 2008).

ABCC6 is built of 31 exons and encompasses in total 73 kb. Its mRNA is 6 kb in size and has an open reading frame of 4.5 kb. The gene codes for the protein *ABCC6* (multidrug resistance-associated protein 6) with a

total number of 1503 amino acids (Plomp et al., 2008; Chassaing et al., 2005).

More than 180 *ABCC6* mutations are known to date. The predominant mutation in European patients is p.R1141X, c.3421C > T with an occurrence of >25% in a Dutch (Hu et al., 2003a) and German (unpublished data) cohort. In the US, a large deletion of several exons (del23-29) is predominant (Saux et al., 2001).

A founder effect can be assumed, especially for South African Afrikaners (predominantly Dutch settlers), which show a high prevalence of p.R1141X haplotypes (Le Saux et al., 2002; Torrington and Viljoen, 1991).

ABCC6 is mainly expressed in the liver, where the protein can be found in the basolateral membranes of hepatocytes. It is also expressed to a lesser extent in the kidney (proximal tubular cells) and the gastrointestinal tract (Kool et al., 1999; Matsuzaki et al., 2005).

Another gene that can cause PXE is the ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*), which may also cause generalized arterial calcification of infancy type 1 (OMIM 208000) and type 2 (OMIM 614473) (cf. Chapter 7 – differential diagnoses) (Ralph et al., 2022; Rutsch et al., 2003).

Histopathologic studies of BrM calcification are limited due to the scarcity of donor eyes in this rare disease. Early findings in donor eyes with AS report patchy areas with basophilia in BrM, indicating calcium deposits (Hagedoorn, 1939; Bö and ck, 1938; Verhoeff and Sisson, 1926). Klein proved the presence of calcium in BrM in 1947, and also discovered that BrM was often fragmented in the calcified areas, similar to the skin lesions (Klein, 1947). Later it was discovered that calcium deposits consisted of calcium phosphates, including hydroxyapatite (HAP) (Jensen, 1977). A later study suggested damaging of the collagen fibres as well, besides the well known calcification of the elastic fibres (Gheduzzi et al., 2003).

Gorgels et al. developed an *Abcc6*^{-/-} mouse as an animal model to study BrM calcification without the need for scarce human tissue (Gorgels et al., 2005). They found BrM calcification of the elastic layer, but also a network of calcified collagen fibres (Gorgels et al., 2005, 2012).

A recent study with six PXE postmortem eyes showed extensive deposition of hydroxyapatite throughout the BrM, including both the elastin layer and the collagen layers. The topographical distribution of HAP deposition correlated with the clinical phenotype. The so called ‘Area 2’ or ‘coquille d’oeuf, which is hyperreflective on near infrared imaging, corresponded with dense precipitation in the posterior pole (Charbel Issa et al., 2010; Risseeuw et al., 2023).

BrM calcification is also common in ageing. Van der Schaft found calcification of the elastic layer of BrM in the majority of donor eyes older than 33 years (van der Schaft et al., 1992). On a postmortem wholemount, this was visible as snowflake-like precipitations in the posterior pole. BrM calcification is associated with age-related macular degeneration (AMD), especially neovascular AMD (Spraul and Grossnihlatis, 1997; Green and Enger, 1993). Calcification of the elastic layer makes it prone to fragmentation and focal breaks, which ultimately may lead to the ingrowth of secondary CNV (Spraul and Grossnihlatis, 1997; Chong et al., 2005; Spraul et al., 1999). These similarities between AMD and PXE suggest that PXE can be used as a prototype disease to study pathological BrM calcification in ageing.

5. Disease mechanism

Transplantation studies and parabiotic heterogenetic pairing in a mouse model confirmed that PXE is a metabolic disease attributable to circulatory factors such as inorganic pyrophosphate (PPI) (Jiang et al., 2009, 2010).

5.1. *ABCC6* and pyrophosphate

In the liver, the *ABCC6* protein is localized to the basolateral

membrane of hepatocytes and promotes the excretion of adenosine triphosphate (ATP) (Jansen et al., 2013). Subsequently, the membrane-bound, extracellular ENPP1 protein hydrolyzes ATP to AMP and PPI in the extracellular space (Jansen et al., 2013, 2014a). As a result, plasma PPI – a critical inhibitor of ectopic calcification – is reduced in PXE patients (Dedinszki et al., 2017; Pomozi et al., 2017; Jansen et al., 2014b; Kauffenstein et al., 2018).

5.2. Other potentially involved proteins

Tissue-nonspecific alkaline phosphatase (TNAP) hydrolyzes PPI into inorganic phosphate (Pi), a promotor of soft-tissue calcification. Interestingly, PXE patients were shown to have higher TNAP activity compared to controls, leading to decreased PPI levels, which might aggravate soft tissue calcification (Sánchez-Té et al., 2019). Conversely, reducing TNAP activity in *Abcc6*^{-/-} mice attenuates soft tissue calcification (Li et al., 2019a).

CD73 protein, encoded by the 5'-ectonucleotidase (*NT5E*), converts adenosine monophosphate (AMP) to Pi and adenosine, which is an inhibitor of TNAP. Bi-allelic mutations in *NT5E* were shown to result in lowered adenosine levels and thus increase TNAP activity. This also results in a soft tissue calcification disorder (Arterial Calcification Due to Deficiency of CD73 [ACDC]) (St. Hilaire et al., 2011a) (Fig. 1).

6. Histology

Ocular alterations in PXE appear to be a result of an increased calcification, associated with increased thickness in BrM.

Histopathologic correlates have been described for several ophthalmologic features in PXE.

Hagedoorn reported degeneration of the elastic fibers of Bruch's layer with the consequence of impaired translucency, which is the cause of the grey or dotted appearance of the fundus. Further, he described that AS are ruptures in the degenerated BrM (Hagedoorn, 1939, 1975).

Other studies of BrM calcification are limited. Early investigations have shown calcification of collagen layers in BrM, resulting in fragmentation and thickening of the layers (Gheduzzi et al., 2003; Gorgels et al., 2005, 2012).

A recent study on six PXE postmortem eyes showed extensive deposition of hydroxyapatite throughout the BrM, including both the elastin layer and the collagen layers (Risseeuw et al., 2023). The topographical distribution of HAP deposition correlated with the clinical phenotype. The so called coquille d'ouf, which is hyperreflective on near infrared imaging, corresponded with dense precipitation in the posterior pole (See Fig. 3). There was gradual change towards the midperiphery where the HAP precipitation was more intermittent. Interestingly, in the locations where calcification was intermittent, it was situated above the vascular lumen of the choriocapillaris, which suggest that the process of BrM calcification might be linked to systemic factors such as PPI.

The thorough study correlating OCT images with post-mortem tissue samples showed that the elastic layers are especially heavily affected. Specifically, extensive calcium-phosphate deposition was found, visible as a meshwork-like pattern. Spatially, the depositions are denser centrally than peripherally. Ion mass spectrometry implies the deposits consist of inorganic HAP (Risseeuw et al., 2023).

Although HAP can also be found in aged controls and other diseases such as age-related macular degeneration, the histological spatial distribution in PXE mirrors the clinical phenotype (Chong et al., 2005). Specifically, confluent meshwork-like calcification in BrM was found in more central areas, followed by a transition zone of intermediate calcification (Risseeuw et al., 2023).

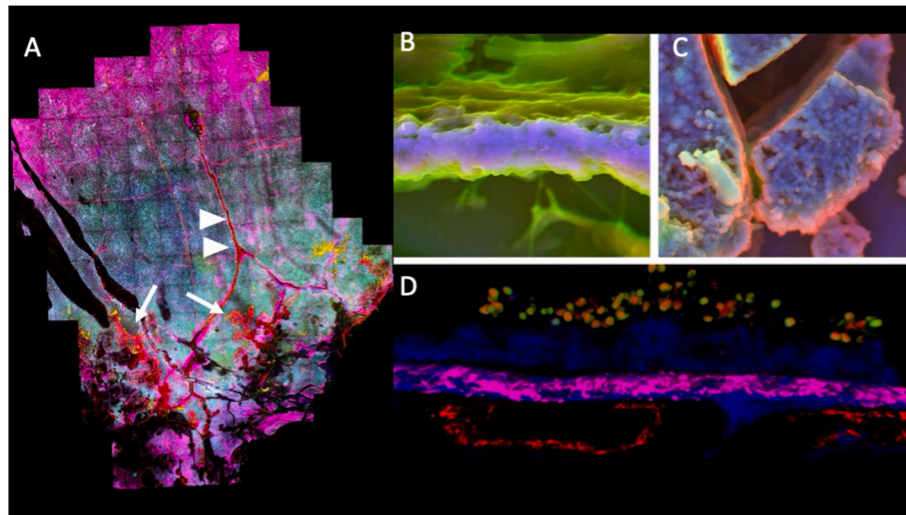


Fig. 3. Histology of ocular alterations in Pseudoxanthoma elasticum (PXE)

The flatmount of a human donor eye (A) shows the spatial distribution of alterations in eyes with PXE. Centrally, late stages including atrophic areas and choroidal neovascularization (white arrow) is visible. Angioid streaks (white arrowheads) radiate towards the periphery, where they terminate around the Peau d'orange (peripheral pink area). Electron microscopy (B–D) reveals an altered ultrastructure of Bruch's membrane, highlighting hydroxyapatite (HAP) deposits with the elastic and collagen layers.

7. Clinical presentation

7.1. Ophthalmologic characteristics

As a first-order approximation, the ophthalmic manifestations of PXE can be grouped into two categories: PXE-specific lesions and secondary complications shared with other BrM diseases. Notably, the secondary complications are similar to late AMD. This distinction of lesions is critical for defining biomarkers that reflect disease progression versus biomarkers linked to the severity of secondary complications.

7.1.1. Distinct morphologic characteristics

7.1.1.1. Peau d'orange and confluent calcified BrM

7.1.1.1.1. Clinical characteristics. Peau d'orange is typically described as an area with a 'granular/dotted' aspect. In the affected area, greyish spots conceal the orange choroidal reflex (Fig. 2). Peau d'orange is the earliest ophthalmic clinical sign in PXE, even preceding AS (Shimizu, 1961; Mansour et al., 1993; Krill et al., 1973). Toward the center, peau d'orange becomes confluent in the form, which was originally termed as the 'grey zone' (referred to as confluent calcified BrM in this article) (Grönblad, 1958).

Clinically, peau d'orange is more noticeable in eyes with greater choroidal pigmentation. It was previously believed that the temporal area was the primary location for peau d'orange. However, Charbel Issa and colleagues have suggested that peau d'orange is possibly just more prominently visible in this region (Charbel Issa et al., 2010).

Centrifugal progression of peau d'orange with age was already described in early clinical reports (Grönblad, 1958). Risseuw et al. have recently quantified the temporal dynamic of these zones, with the central border of peau d'orange shifting towards the periphery over time. This rate was 0.07–0.12-disc diameters per year (i.e., approx. 0.17 $\mu\text{m}/\text{year}$), depending on the age at the start of the observation. The temporal border does not seem to change over time and has been described as the area to be 'predisposed' for calcification (Fig. 4) (Risseuw et al., 2021).

7.1.1.1.2. Histopathology. Peau d'orange delineates the transition from a calcified to an uncalcified BrM (Risseuw et al., 2023). Typically, this transition is observed first close to the optic disc and then progresses towards the periphery (Guzey et al., 2001; Grönblad, 1958). The reason

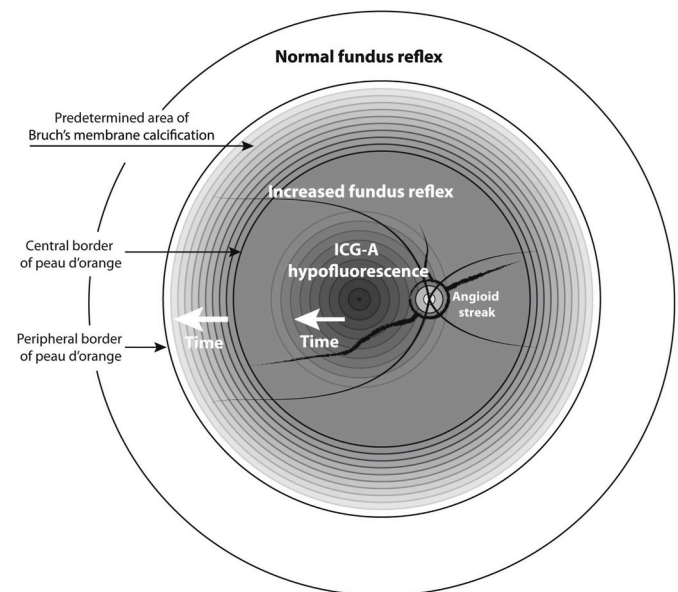


Fig. 4. Zones of calcification

The diagram illustrates the current knowledge on fundus alterations in pseudoxanthoma elasticum, combining observable changes across various imaging methods. In the initial stages of the disease, a (possibly predetermined) region exhibiting Bruch's membrane (BrM) calcification, characterized by a speckled appearance referred to as peau d'orange, is already evident. Gradually, this area undergoes a progression of more cohesive BrM calcification, manifesting as an augmented fundus reflex. Over time, a discernible pattern emerges in the form of reduced indocyanine green angiography (ICG-A) fluorescence, initiating in the macula and extending centrifugally. This model was initially proposed by Charbel Issa et al. and was modified by Risseuw et al.

for this process is not fully understood yet. However, pathological analysis has revealed that the BrM is markedly thinner in the central region than in the peripheral region. This difference in BrM thickness may explain why the BrM in the macula region is more vulnerable to calcification (Chong et al., 2005).

7.1.1.1.3. Imaging. The area of calcified BrM, that is visible on funduscopy can be visualized more clearly by near-infrared reflectance

(NIR) imaging. BrM calcification leads to a hyperreflective area centered on the posterior pole. The border to the 'normal' reflectance in the periphery is characterized by a mottled appearance of hyper- and normal reflectance and co-locates with peau d'orange on funduscopy.

In OCT imaging, BrM shows small hyperreflective lesions (Gliem et al., 2013a).

In color fundus photography, peau d'orange and confluent calcified BrM are visualized most clearly in the red channel (Spaide, 2015).

Indocyanine green angiography (ICGA), which uses a longer excitation wavelength (i.e., 740–800 nm), can also be used to visualize sub-RPE changes.

Interestingly, transition zones visible in ICGA differ from the transition zones seen with the other imaging modalities. According to Charbel Issa et al., a border of reduced fluorescence in the ICGA late-phase is located slightly central to the peau d'orange outer boundary. As a result, three areas can be described: area 1 with a reduced fluorescence in ICGA late-phase and increased reflectance in NIR; area 2 with an increased reflectance in NIR, but a normal ICGA late-phase signal; and area 3 characterized by clinically normal retina (Fig. 4) (Charbel Issa et al., 2010).

Short wavelength (blue or green light) autofluorescence (FAF), which mostly depicts fluorophores in the outer retina and RPE, shows no transition zone in the area of peau d'orange (Charbel Issa et al., 2010).

7.1.1.2. Angioid streaks

7.1.1.2.1. Clinical characteristics. AS are a classic feature but not pathognomonic for PXE. They occur in various systemic diseases, including Sickle cell disease, Thalassemia, Paget disease (Saito-Hakoda et al., 2023; Goldberg et al., 1971; Hamilton et al., 1981; Lubega et al., 2015; Jampol et al., 1987). In PXE, angioid streaks are the most commonly (reported) finding and are reported to be present in all patients 20 years after diagnosis (Georgalas et al., 2011).

AS received their name due to their vessel-like appearance on funduscopy. They are typically located around the optic disc and radiate toward the periphery, while they can be divided into branches during their course. They are broadest around the optic disc and become shallower during their course to the periphery (Hagedoorn, 1939; Finger et al., 2009a). It is assumed that angioid streaks develop as a consequence of mechanical stress exerted on the eye.

While angioid streaks follow mostly a radial pattern, they can also follow a circumpapillary pattern. In addition, vertical streaks temporal to the fovea between the insertions of the superior and inferior oblique muscle have been reported (Georgalas et al., 2011; Krümmel, 1950).

AS are confined to the area of calcification (i.e., areas 1 and 2 defined by Charbel Issa et al.) and typically do not cross peau d'orange (Charbel Issa et al., 2010; Risseuw et al., 2020, 2021). They prolong over time and extend further to the periphery parallel to the enlargement of the calcified area (i.e., parallel to the peau d'orange movement toward the periphery). Additionally, their length is an indirect surrogate for the severity of BrM calcification and is associated with the extent of macular degeneration (Risseuw et al., 2020, 2021).

7.1.1.2.2. Histopathology. AS represent breaks in the calcified BrM with degeneration of the overlaying retinal pigment epithelium. The histopathology also explains the limitation of AS to the calcified area (Risseuw et al., 2023).

AS are a risk factor for developing exudative neovascularization. Recent imaging studies show that also non-exudative neovascularization is frequently evident along AS (Marques et al., 2021; Corbelli et al., 2018).

7.1.1.2.3. Imaging. On OCT, AS are visible as breaks in BrM (Fig. 2) and can often be followed through different B-scans (Risseuw et al., 2021).

AS appear dark on FAF, due to the disruption of BrM and RPE. Along the course of the streaks, hyperautofluorescent spots or areas can be present, termed 'parastreak phenomenon'. Finger et al. showed that

these areas correspond to hyperpigmentation on fundus photography and that the phenomenon was most predominant in eyes without CNV (Finger et al., 2009a).

Marchese and coworkers observed different patterns of AS on FAF imaging, ranging from simple hypoautofluorescence in young patients, over parastreak phenomenon in middle-aged patients to extensive peripapillary atrophy in older patients. Although this was a cross-sectional study, it hints on a restructuring process that AS are undergoing (Marchese et al., 2017).

On fluorescein angiography, AS exhibit a late staining that varies in intensity depending on the width of the streak, as described by several authors reviewing angioid streaks. If extensive or associated with atrophy, a window defect is present.

7.1.1.3. Comet (tail) lesions. Comet tail lesions or (in the absence of a tail) comet lesions, are visible on funduscopy as white punched-out lesions, often with a tail pointing toward the optic disc, mostly located in the mid-periphery. Less frequently, they are located around the optic disc and can also appear clustered as 'comet rain' (Murro et al., 2018). Of note, the location is outside of the calcified area and can aid in differentiating PXE from other retinal degenerations (Gliem et al., 2013a; Gass, 2003b; Finger et al., 2009b).

Funduscopy, they facultatively exhibit pigment, putatively from RPE-clumping at the edge of the comet. On OCT, they present as hyperreflective spherules with a hyporeflexive core, with some phenotypic overlap to outer retinal tubulations (Murro et al., 2018; Ricciotti et al., 2023).

On fluorescein angiography, comet tail lesions appear hyperfluorescent with variable hyperfluorescence of the tail pointing towards the optic disc (Gliem et al., 2013a; Finger et al., 2009b; Federman et al., 1975; Lafaut et al., 1998). In peripheral areas, they are found as round lesions in the outer retina visualized on B-scans, while smaller, putatively 'early' comet lesions are still connected to the RPE-BrM (Murro et al., 2018).

7.1.1.4. Pattern dystrophy and detachment of the neurosensory retina

7.1.1.4.1. Clinical characteristics. Pattern dystrophy ('pattern dystrophy-like changes') in PXE has been reported in the 1960s and 1970s (Smith et al., 1964; Shiraki et al., 2001; von Winning and Oosterhuis, 1974). McDonald et al. described the lesions as 'pigment clumps' resembling a 'string of pearl' connected to the optic disc (McDonald et al., 1988). Later, frequencies between 10% and >70%, (even up to 100% in very small cohorts) were reported (Agarwal et al., 2005; Finger et al., 2009a). This wide span might also be caused by the imaging modalities used for detection and differences in definition.

Argawal et al. showed in a more comprehensive investigation that all 5 subtypes of pattern dystrophy described previously were present in a PXE cohort (Agarwal et al., 2005). A possible association of pattern dystrophy-like changes and increased risk for CNV development has been hypothesized but needs further evaluation in longitudinal studies (Finger et al., 2009a). Pattern dystrophy-like changes are associated with a larger extent of BrM calcification, which is also a risk factor for macular degeneration (Risseuw et al., 2020).

7.1.1.4.2. Imaging. Pattern dystrophy can be best visualized using fundus autofluorescence imaging as hyperfluorescent patchy regions.

In OCT, areas with pattern dystrophy often show a subtle detachment of the neurosensory retina from the RPE with outer segments that 'dangling' into the enlarged sub-neuroretinal space (Gliem et al., 2013a; Issa et al., 2009).

7.1.1.5. Optic disc drusen. Drusen of the optic nerve head are reported with a frequency of 6% up to 25% (Finger et al., 2009a; Meislik et al., 1979; Pierro et al., 1994; Pipelart et al., 2019) of PXE eyes. This is a significantly higher rate compared to the general population (prevalence ~0.3%) (Auw-Haendrich et al., 2002).

On FAF imaging, they appear hyperautofluorescent. Their clinical manifestation can range from buried drusen, that are not visible on FAF, but can be revealed by ultrasonography, up to confluent 360° optic disc drusen (Fig. 5).

Pathologically, they represent a swelling of nerve fibers resulting in cystoid bodies with facultative calcification, hypothesized to be caused by the slowing of axoplasmic flow within the fibers (Auw-Haedrich et al., 2002; Palmer et al., 2018; Friedman et al., 1975).

The reason for the increased incidence of this lesion in PXE can only be speculated and includes the possibility of a calcified BrM as an impairment for the normal axoplasmic flow.

Optic disc drusen have been shown to have a functional impact due to an increased rate of ganglion cell layer degeneration in eyes with PXE and optic nerve head drusen, compared to PXE without this lesion and controls. It must be noted that the authors also found an increased rate of ganglion cell layer thinning over time in eyes with PXE without optic disc drusen, indicating possible primary damage with optic disc drusen as a consequence of the compression at the disc itself or during the early course of the optic nerve (Hess et al., 2021a). However, further studies are needed to clarify the pathogenesis and functional impact of optic disc drusen in PXE.

7.1.1.6. Multiple evanescent white dot syndrome (MEWDS)-like acute retinopathy

7.1.1.6.1. Clinical characteristics. In rare cases, PXE patients can develop an acute retinopathy that shares clinical characteristics with multiple evanescent white dot syndrome (MEWDS). This acute retinopathy is hypothesized to arise from retinal autoantibodies. Typically, patients report symptoms ranging from blurred vision, photopsia to loss of central vision (Gliem et al., 2019).

7.1.1.6.2. Imaging. Using slit-lamp examination, vitreous cells may be seen. In addition, on funduscopy, white dots are typical. In OCT,

localized, patchy loss of the ellipsoid zone is characteristic. On FAF, these patchy lesions are initially hyperautofluorescent, due to the absence of photoreceptor outer segments (rhodopsin) that partially reduce the FAF signal (Gliem et al., 2019). With prolonged FAF imaging (i.e., bleaching of the surrounding retina), the contrasts between the lesions and the surrounding fades.

7.1.2. Age-related macular degeneration-like characteristics

7.1.2.1. Reticular pseudodrusen. Reticular pseudodrusen (RPD or sub-retinal drusenoid deposits [SDD], Fig. 6), are present in more than 50% of PXE patients, mostly present in their mid-50s. RPD are not present in very early stages of PXE (Gliem et al., 2015a). This is similar to other BrM diseases such as AMD, Sorsby Fundus Dystrophy, and late-onset retinal degeneration (Gliem et al., 2015b; Cukras et al., 2016). This indicates that RPD are an unspecific expression of a diseased BrM, temporarily visible in intermediate disease stages. Diseases with RPD often show impaired rod-mediated dark adaptation (including PXE), and eventual development of RPE atrophy or CNV (Finger et al., 2014; Nigalye et al., 2022).

7.1.2.2. Choroidal thinning and choriocapillaris loss. A significantly thinner choroid has been described for PXE, compared to controls (Gliem et al., 2014). Later, the availability of optical coherence tomography angiography (OCT-A) allowed for more detailed analyses of choriocapillaris loss (Hess et al., 2021b). Both studies found more pronounced alterations closer to the optic disk compared to the temporal macula. Further, substantial choriocapillaris loss on OCT-A can be present prior to choroidal thinning on OCT and the progression of flow-deficits with increasing age is more pronounced in PXE compared to controls (Loewinger et al., 2023).

Again, choroidal thinning and choriocapillaris loss is also a feature in

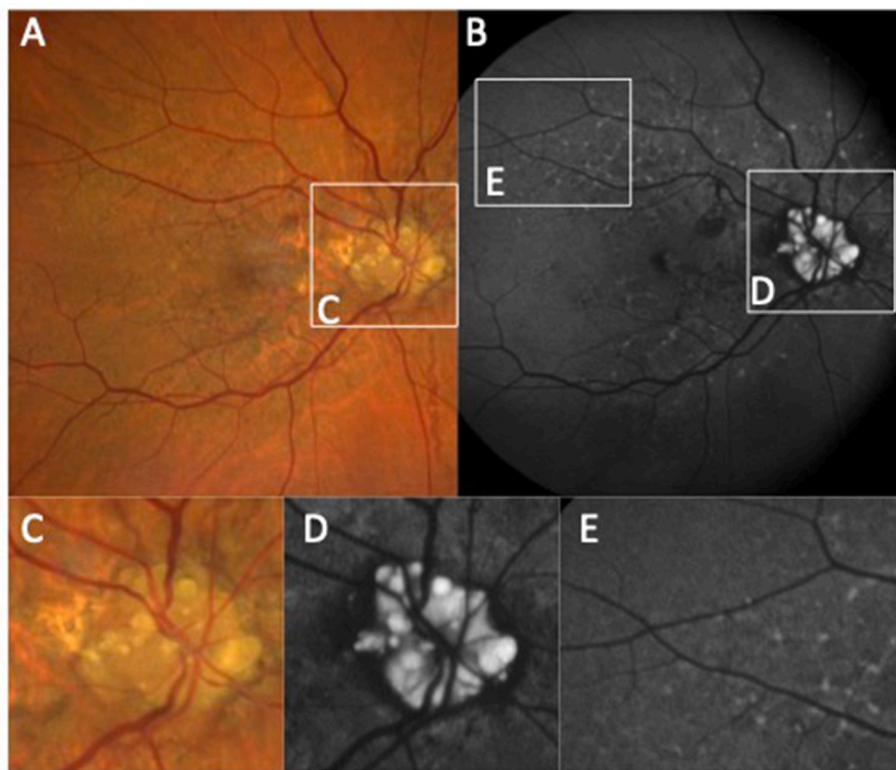


Fig. 5. Facultative ocular findings in Pseudoxanthoma elasticum

On funduscopy (A, C) several common and facultative findings in PXE are visible. Optic disc drusen affecting all quadrants of the optic nerve head are present. On short-wave fundus autofluorescence (B, D, E) optic disc drusen are strongly hyperautofluorescent (D). Additionally, pattern dystrophy-like changes can be found around the vessel arcades (E).

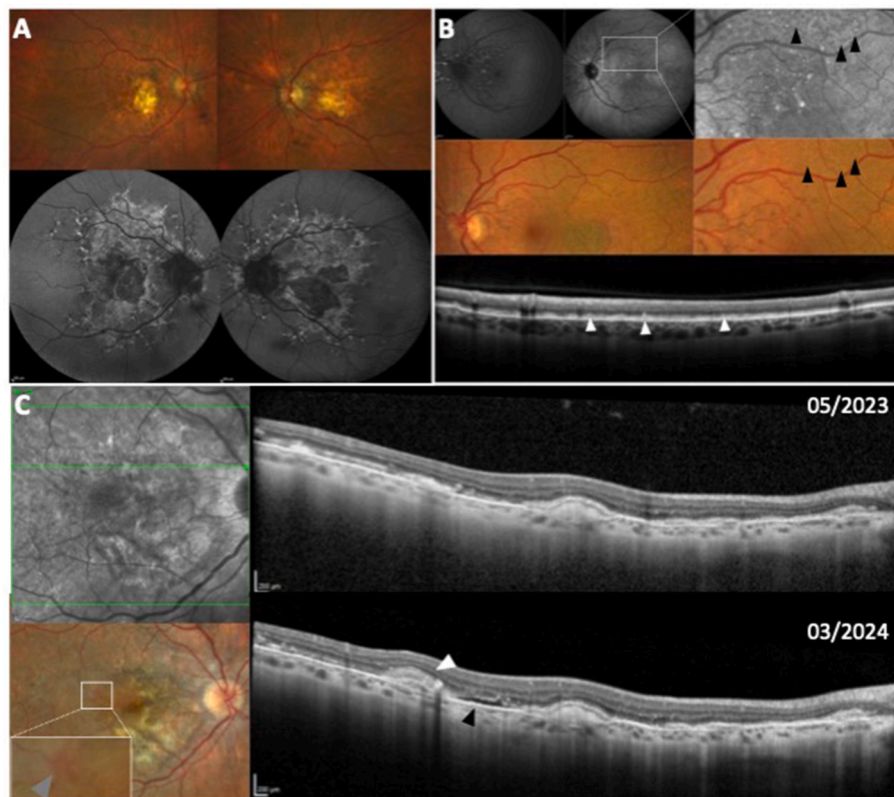


Fig. 6. PXE-associated lesions with phenotypic overlap to Age-related macular degeneration (AMD). A – Chorioretinal atrophy. Atrophy develops in late stages of PXE as well as in AMD. While on fundus photography (A, upper row) the atrophy appears well defined. Fundus autofluorescence (A, lower row), however, reveals extensive alterations including pattern dystrophy and generalized hyperautofluorescence around the hypoautofluorescent atrophy, distinguishing it clearly from AMD. B – Reticular pseudodrusen (RPD). RPD can be best depicted on infrared reflectance (B, upper row, 2nd and 3rd image) and depict as circular lesions with hyperreflective core (black arrowheads) and on fundus photography as leopard-like yellow spots. On Optical coherence tomography B-Scans (B, lowest row), bumpy alterations above the RPE at the axial location of photoreceptors can be shown (white arrowheads). C – Choroidal neovascularization. CNV with or without exudation typically appears along the course of angioid streaks. In PXE, CNV are mostly Type 2 lesions or mixed Type 1/Type 2 lesions, appearing with an RPE elevation and an ill-defined hyperreflective lesion above (white arrowhead). In case of intraretinal or subretinal exudation (black arrowhead), anti-VEGF treatment is indicated. On fundus photography, a red aspect from the CNV or a mild bleeding is visible (grey arrowhead).

BrM diseases (especially in the presence of RPD), including Sorsby Fundus Dystrophy and late-onset retinal degeneration, as well as AMD (Cukras et al., 2016; Hess et al., 2021b; Borooah et al., 2009; Borrelli et al., 2017; Muller et al., 2018).

7.1.2.3. Choroidal neovascularization. As in AMD, CNV (Fig. 6) is highly prevalent and a major cause of vision loss (Risseuw et al., 2021; Nigalye et al., 2022; Gliem et al., 2014). In contrast to AMD, CNV occurs at younger ages (median 55 years of age) and is often bilateral (Finger et al., 2009a; Risseuw et al., 2019; Gliem et al., 2016a; Raming et al., 2024). A recent study showed that bilateral treatment is necessary in 64.2% (Raming et al., 2024).

CNV is typically co-localized to angioid streaks as these breaks in BrM are a vulnerable site for vessel ingrowth from the choroid (Gliem et al., 2013b).

Previous studies of CNV due to angioid streaks (without confirmation of the underlying disease) showed that Type 2 CNV, expanding between the RPE and the photoreceptors, is more common than Type 1 CNV. Further, eyes with Type 2 CNV exhibited a worse visual prognosis (Gliem et al., 2013b; Nakagawa et al., 2013; Mimoun et al., 2010).

7.1.2.3.1. Imaging. Fluorescein angiography used to be the primary method for detecting exudation from CNV in PXE. However, due to the excellent performance of OCT in visualizing leakage (subretinal and intraretinal fluid) as well as type 1 and type 2 CNV, OCT has become the most important imaging techniques. In CNV secondary to PXE, the break in BrM can often be detected if the scan pattern is dense.

7.1.2.3.2. Treatment. To date, CNV is the only ophthalmic characteristic of PXE that is amenable to therapeutic intervention. Intravitreal anti-VEGF injections have been proven effective, with comparable results to AMD eyes (Gliem et al., 2020a; Finger et al., 2008, 2011a; Mimoun et al., 2010). Based on clinical experience, all anti-VEGF agents are effective for treating exudative CNV in PXE. However, efficacy data in PXE patients (among other rare diseases) from a sham-controlled phase 3 trial is only available for Ranibizumab (Lai et al., 2018).

In addition, efficacy data from other PXE-specific prospective but uncontrolled studies is available for Ranibizumab and Bevacizumab (Finger et al., 2008, 2011a, 2011b). Aflibercept was also investigated in a non-randomized, open-label, uncontrolled prospective trial and showed efficacy for treating CNV in PXE (Gliem et al., 2020a).

Although CNV in PXE is treatment-intensive, there is no data on 'prophylactic' or 'life-long' anti-VEGF treatment. As in other diseases, treatment decision should be taken with care but initiated immediately if necessary.

Importantly, two specific findings that are not amenable to anti-VEGF treatment are non-exudative neurosensory detachment (cf., section on pattern dystrophy, Chapter 6.1.1.4) and non-exudative CNV (Gliem et al., 2013a; Hess et al., 2020a).

Clinical experience confirmed by a recent investigation shows that non-exudative CNV is a very frequent finding in PXE, especially along Angioid Streaks (Marques et al., 2021). In the median observation period of more than 2 years, the lesions were mostly stable without any treatment, concluding there is no therapy initiation needed in case of

non-exudative CNV detection. The lesions should however be thoroughly evaluated at each follow-up.

Other therapeutic approaches for CNV than anti-VEGF, such as photodynamic therapy, are outdated and should not be used as a first-line therapy due to unfavorable results (Rohart et al., 2022).

The visual prognosis of CNV in PXE is overall good if the initial visual acuity is preserved (i.e., if the therapy is started early). Patients with reduced visual acuity at the event of exudation and atrophy show a more unfavorable outcome. (Raming et al., 2024; Rohart et al., 2022).

The risk of CNV increases with age, with a median age of onset in PXE in their mid-50s.¹²⁴¹³²

7.1.2.4. Macular atrophy. Atrophic areas develop mostly within the macular area, can be of multifocal or unifocal aspect, and confluent over time. In a cross-sectional study, the prevalence of atrophy in PXE was 30%, but significantly higher in patients older than 60 years (Gliem et al., 2016a).

According to Gliem and co-workers, atrophy and CNV are usually present concurrently. In all eyes with atrophy but no CNV, pattern dystrophy-like changes were found, indicating a risk factor for atrophy development. Further, the progression of atrophy in eyes with no CNV was faster ($3.3 \pm 1.3 \text{ mm}^2/\text{year}$) than in those with CNV ($1.6 \pm 1.1 \text{ mm}^2/\text{year}$) (Gliem et al., 2016a).

Compared to other diseases with angioid streaks as a clinical finding, patients with PXE show an increased rate of atrophy progression (Rohart et al., 2022).

Often, a mix of atrophic areas and fibrovascular scars can be found in late stages, especially in older patients who did not have access to anti-VEGF therapy when their exudation initially started (Gliem et al., 2016a).

7.1.3. Visual function

7.1.3.1. Visual acuity. In a Dutch cohort, a significant reduction in visual acuity was observed in the 5th decade of life in PXE patients. Any form of visual impairment was found in over a third (36.9%) of the cohort, and legal blindness was observed in 15.4% (Risseeuw et al., 2019).

However, it must be considered that anti-VEGF injections to treat the (frequent) complication of secondary CNV have only been existing since the early 2000s, leaving older patients with an onset of CNV before that time without treatment (Gragoudas et al., 2004). The availability of anti-VEGF will most likely result in better visual outcomes in older patients in the future.

Reduced visual acuity due to subfoveal exudative CNV, is often a reason for ophthalmologic consultation, sometimes even before the diagnosis PXE is given. However, when specifically asked for it, dark adaptation problems are often reported as first symptom, without the patients being aware of its relevance.

Permanent central vision loss is present in later stages of the disease, either due to CNV or exudation from the CNV located in the subfoveal area, or due to atrophic changes extending towards the fovea.

The presence of CNV can cause varying degrees of visual deterioration. Treatment with anti-VEGF can usually preserve visual acuity, but long-term outcomes may vary (Mimoun et al., 2010; El Matri et al., 2011; Tilleul et al., 2016; Shah and Amoaku, 2012). Outdated treatment options such as laser coagulation and photodynamic therapy (PDT) monotherapy have resulted in worse outcomes (Gliem et al., 2013b; Browning et al., 2005; Heimann et al., 2005; Chan et al., 2010; Arias et al., 2006; Lee et al., 2007).

7.1.3.2. Peripheral visual field. Very little data is published on visual fields in PXE. Constricted visual fields are reported in the presence of optic disc drusen (Meislik et al., 1979; Hess et al., 2021a; Shields et al., 1975; Yap et al., 1992). Progressive visual field constriction was

reported in individual cases (Hess et al., 2021a).

7.1.3.3. Dark adaptation. Very frequently, PXE patients report difficulties in dark adaptation. This includes difficulties in cone-mediated dark adaptation (e.g., 'driving during the day into a poorly illuminated tunnel') and rod-mediated dark adaptation (e.g., 'going for a walk at night') (Hess et al., 2020b).

These alterations were objectified with dark adaptometry and revealed pronounced alterations of the rod-mediated phase of dark adaptation. While some patients showed a slowed kinetic but reached the final threshold within the testing time of 30 min, some patients did not reach a final threshold comparable to controls within this testing time. A 'local Vitamin A deficiency' at the level of the photoreceptors was postulated due to the mineralized BrM serving as an increased barrier between systemic blood circulation and RPE/photoreceptors. Vitamin A levels were within normal ranges in all patients, but an exploratory supplementation of Vitamin A in 2 patients improved dark adaptation after 4 weeks (Hess et al., 2020b).

This partial reversion leads to the conclusion that the dysfunction results from an altered barrier between the delivery of visual cycle substrate (i.e., choroid and systemic circulation) and 'consumer', namely photoreceptors and RPE and not from dysfunction of the RPE and photoreceptors alone.

7.1.3.4. Mesopic and scotopic steady-state dysfunction. Apart from kinetic dysfunction (i.e., dark adaptation delay), steady-state mesopic and scotopic function is impaired in PXE, too.

Low luminance visual acuity is significantly worse in PXE compared to controls, and the Low Luminance Deficit (LLD, i.e., the difference between best-corrected visual acuity [BCVA] and Low-luminance visual acuity [LLVA]) was comparable to reported LLDs for intermediate AMD (Hess et al., 2020b; Wu et al., 2016). In line with this, low-luminance-related quality of life was significantly reduced in this cohort. No significant correlation between LLVA (or LLD) and Dark adaptation was found, in line with findings in other retinal diseases, indicating that an interplay of cell mechanisms is responsible for the dysfunction.

More unanticipatedly, contrast sensitivity was impaired despite a visual acuity of 0.5 or 20/40 Snellen (i.e., 0.3 logMAR) (Hess et al., 2020b).

Mesopic microperimetry is impaired in PXE patients. Sensitivity loss follows the spatial distribution of BrM mineralization: the largest degree of dysfunction is found close to the optic disc, and less dysfunction is present in the periphery (Hess et al., 2020a).

Scotopic cyan and scotopic red sensitivity losses are even larger than mesopic loss. Point-by-point analysis reveals that rod-mediated sensitivity loss can occur in isolation, while cone-mediated sensitivity loss is only evident at locations with severe rod-mediated sensitivity loss. This relationship implies a temporal sequence of rod sensitivity loss preceding cone sensitivity loss (Hess et al., 2020a).

7.2. Dermatologic characteristics

Individuals who notice variations in their skin typically seek medical assistance and confer with healthcare professionals. Dermatologists play a vital role in identifying PXE, as they are frequently the first to detect the ailment and collaborate with other medical fields to manage the condition in a multidisciplinary approach.

Earliest alterations usually appear in childhood on the neck and flexural areas and consist of uncolored or slightly yellowish papules in a reticular pattern and 1–5 mm of size. They coalesce over time to form larger plaque-like areas (Fig. 7). Further involved areas are the axillae, inguinal regions, antecubital and popliteal fossae, and periumbilical area.

In extreme cases, the skin becomes very lax and abundant skin can be



Fig. 7. Skin alterations in Pseudoxanthoma elasticum

Dermal alterations are often best and first visible at the back of the neck. The inner sides of the elbows and other intertriginous areas are affected. The mucosa of the inner lip can be altered with whitish lesions.

found, leading to cosmetic restraints to the patients (Marconi et al., 2015; Utani et al., 2010; Reeve et al., 1979).

Further, mucosal areas such as the gingiva and mucosa of the lower lip are frequently altered with whitish telangiectatic plaques (Hu et al., 2003b; Li et al., 2009, 2019b; Li and Uitto, 2018). A frequency of more than 83% is reported in a case series of 18 patients (Nozzi et al., 2008).

Histologically, the mid-epidermis is altered, while adjacent layers appear normal. Best visible on Von Kossa staining, the elastin band appears bloated due to the splitting and curling of elastin fibers. Histochemically, abnormal calcium depositions (CaCO_3 , CaPO_4) can be found (Ross et al., 1978).

7.3. Cardiovascular characteristics

Cardiovascular manifestations of PXE are characterized by lesions resembling premature atherosclerosis, with the consequence of rare early myocardial infarcts and more frequently cerebrovascular events (van den Berg et al., 2000; Leftheriotis et al., 2013).

Ischemic stroke and transient ischemic attacks are more frequent events, with a 3.6 times higher relative risk for ischemic stroke in PXE patients under 65 years (van den Berg et al., 2000; Kauw et al., 2017). The prevalence of ischemic strokes in a Dutch cohort was reported to be 8% compared to 3% in a comparable non-PXE cohort. Similarly, transient ischemic attacks (TIAs) were more prevalent in the PXE cohort (7% vs. 2%) (Kauw et al., 2017). Bilateral or unilateral carotid hypoplasia are also more frequently observed in PXE than in the general population (9% versus 0.2%) suggesting developmental implication of yet undefined mechanism. These vascular abnormalities are frequently associated to intracranial aneurysm as a possible complication of high flow in the derivative vessels (Omarjee et al., 2019a).

Compared to hospital controls, calcification of the peripheral artery wall (also termed mediocalcosis) is a cornerstone observation in PXE and more prevalent in the arteries of the arms, intracranial internal carotid artery, the femoral-popliteal arteries and the subpopliteal arteries. Also, the severity of calcification was found higher in the distal limb arteries compared to hospital controls. Similar differences were also found in PXE-patients younger than 55, indicating the importance of immediate

cardiovascular assessment when diagnosing PXE in a patient (Kranenburg et al., 2017).

The prevalence of peripheral artery disease (PAD) in PXE-patients (defined as an ankle-brachial index of <0.9) is 45%, compared to 18% in a much older cohort of 85–89 years (Leftheriotis et al., 2011, 2014).

The histopathological correlates for the majority of findings are a mineralization and secondary fragmentation of the elastic fiber in the internal laminae as well as in the adventitial layers. Cardiac alterations have also been reported (Campens et al., 2013) but the link with PXE remains unclear at present (Biè et al., 2014).

Clinically, vasculopathy in PXE is characterized by reduced or absent peripheral pulse, arterial hypertension, and a low ankle brachial pressure. Patients often report intermittent claudication with variably reduced walking distance and (less frequently) angina pectoris. PAD associated with PXE is generally well tolerated and vascular surgery to restore patency in these patients is not recommended as first-line treatment (Ammi et al., 2015a). To our knowledge, limb amputations have not yet been reported for PXE in the literature.

Due to the implications, the cardiovascular history and counseling for cardiovascular check-up should be proactively considered, also by Ophthalmologists and Dermatologists, when giving the diagnosis PXE.

7.4. Renal involvement

Renal complications in PXE have been underrepresented in the PXE-literature until recently. While only a few cases of kidney stones in PXE patients and sporadic instances of classic nephrocalcinosis were documented in the past, more recent findings have shed light on nephrolithiasis as an underestimated and prevalent feature of PXE (Seeger and Mohebbi, 2016; Letavernier et al., 2019; Ralph et al., 2020; Legrand et al., 2017). A comprehensive examination of renal manifestations in a French cohort, including 113 PXE patients unveiled a striking history of kidney stones in 40% of patients, surpassing by far the incidence in the general population (~ 9 –11%) (Legrand et al., 2017; Trinchieri and Montanari, 2017; Sorokin et al., 2017). Furthermore, computed tomography scans unveiled substantial papillary calcifications, known as Randall's plaques (Letavernier et al., 2018).

A recent review article summarizes the phenotypic overlap between PXE renal involvement and chronic kidney disease (D et al., 2020). Very recently, a cross-sectional comparative study found no difference in prevalence of kidney stones in PXE and hospital controls based on computed tomography (Harmsen et al., 2023). Further studies are necessary to determine the association of retinal alterations and PXE (Ralph et al., 2020).

7.5. Gastrointestinal involvement

Gastrointestinal bleeding is most often reported in young patients, aged 20–30 years. In 1954, Kaplan and Hartmann were the first to provide histopathological evidence that the bleeding is a consequence of connective tissue degeneration in the submucosal arteries of the stomach (Kaplan and Hartman, 1954). However, it is worth noting that Reinertson, Farber, and others have reported a substantial number of cases below the age of 20, accounting for 5 out of 42 cases (REINERTSON and FARBER, 1955). The bleeding episodes are characterized by recurrent, often severe instances of hematemesis (vomiting blood) and melena (dark, tarry stools). While there have been no reported cases of deaths resulting from exsanguination (fatal blood loss), gastrointestinal imaging studies are typically inconclusive (WOO and CHANDLER, 1958; BRANDT, 1961; McCreedy et al., 1989; Dibi et al., 2016). Transfusions may be required in severe cases, but surgical intervention is rarely deemed necessary.

In case of unexplained gastrointestinal bleeding, particularly in younger age groups, PXE should be a differential diagnosis. Epistaxis (nosebleeds), hematuria (blood in the urine), and bleeding from other organs have also been reported, albeit less frequently than

gastrointestinal hemorrhage.

Notably, despite the presence of mineralized elastic fibers in pulmonary tissues, PXE does not exhibit any associated lung phenotype (Yamamoto et al., 1996).

7.6. Pregnancy and fertility

Pregnancy in women affected by PXE has long been a controversial topic. Laymen guidance by a national patient organization has been misleading by connecting pregnancy to overall disease worsening (*Tipps zum Leben mit PXE*). The largest study to date, including 795 pregnancies of 306 women, reports that skin alterations seem to progress during pregnancy, but no evidence is given for disproportional progression of vascular or ocular alterations during pregnancy (Bercovitch et al., 2004). Especially, there is no evidence that avoiding pushing during delivery is necessary.

There might be a mildly increased number of first trimester miscarriages in PXE compared to controls. During pregnancy, a slightly higher percentage reported hypertension (12% in PXE compared to 5–10% in controls), but other complications were not more frequent in PXE (Bercovitch et al., 2004; Lee and Lebwohl, 2021; Berde et al., 1983; Camacho et al., 2016; VILJOEN et al., 1987).

Further, the previous opinion of increased gastrointestinal hemorrhages during pregnancies were not seen in any of the 54 PXE-related pregnancies reported by Viljoen et al. thus were evaluated to be over-reported (VILJOEN et al., 1987).

The placenta exhibits alterations that are often noticed by gynecologists during pregnancy – sometimes even in individuals who were undiagnosed at this point. Alterations include mineralization of the stroma and basement membranes at the maternal site (Wei and Rodeck, 2008; Tan and Rodeck, 2008). Electron microscopy shows an abnormal structure of collagen fibers, as well as mineral precipitates in the extracellular placental compartments, the connective stroma of the villi, and of the chorionic and basal plates (Gheduzzi et al., 2001).

Fertility is unaffected and fetal complications are rare and not significantly more often than in controls (Lee and Lebwohl, 2021; Berde et al., 1983). Since PXE is an autosomal-recessive disorder, the offspring of affected parents will be healthy, apart from very rare cases of pseudo-dominant inheritance, in which one parent is affected, and one is a carrier of a pathogenic *ABCC6* mutation (Charbel Issa et al., 2015).

Genetic counseling for patients of childbearing age might be beneficial to clarify these aspects (Camacho et al., 2016).

8. Differential diagnoses

8.1. Diseases within the pyrophosphate pathway

Several diseases exhibit a multisystemic phenotypic overlap with PXE, including general arterial calcification of infancy (GACI) and deficiency of CD73 (ACDC). Both diseases are rarer than PXE, and their genetic cause results in alterations of the pyrophosphate balance. Specifically, all diseases result in a lower pyrophosphate level due to mutations of different critical actors along the pyrophosphate metabolic pathway (Fig. 1).

8.1.1. General arterial calcification of infancy (GACI)

The *ENPP1* gene encodes for the ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1). This membrane-bound protein hydrolyzes ATP to AMP and PPI. GACI is caused by bi-allelic mutations in the *ENPP1*. The prevalence is estimated to 1:200'000 pregnancies. The overall phenotype, esp. the vascular morbidity, is more severe with a 55% mortality within the first six months of life (Kawai et al., 2022; Rutsch et al., 2008). Ocular alterations appear to resemble PXE with angioid streaks, peau d'orange, and macular hemorrhage as complication based on a single report (Ferreira et al., 2021). Notably, *ENPP1* variants can also cause a classical PXE phenotype (Ralph et al., 2022).

8.1.2. Arterial calcification due to CD73 deficiency (ACDC)

Arterial calcification due to CD73 deficiency, also known as ACDC, is a rare and debilitating disorder in adults. It is caused by mutations in the autosomal recessive *NT5E* gene (St. Hilaire et al., 2011b; Gutierrez et al., 2016; St. Hilaire et al., 2011c). The gene codes for CD73 that hydrolyzes extracellular AMP to adenosine and inorganic phosphate. Adenosine inhibits TNAP. Thus, low adenosine levels in patients with bi-allelic *NT5E* result in increased TNAP activity, which in turn decreases PPI levels. ACDC is characterized by painful and progressive arterial calcifications that primarily affect the lower extremities. Additionally, small joint capsules of the hands and feet may also experience calcifications (St. Hilaire et al., 2011b; Gutierrez et al., 2016; St. Hilaire et al., 2011c). There are about 20 patients currently reported with the disease, with currently no knowledge about the dermatological or ophthalmological phenotype.

8.1.3. Deficiency of Vitamin K-dependent proteins

Vitamin K-dependent proteins in humans include (besides the coagulation factors II, VII, IX, X, and protein C and S) matrix gla protein (MGP); gla-rich protein (GRP); and osteocalcin (OC). The latter three proteins all act as mineralization inhibitors.

Activation of Vitamin K-dependent proteins relies on the endoplasmic enzyme gamma-glutamyl carboxylase (GGCX) and the Vitamin K 2,3-epoxide reductase complex subunit 1 (VKORC1). GGCX modifies Vitamin K-dependent proteins by post-translational carboxylation of glutamate residues into γ -carboxyglutamate, oxidizing Vitamin K in the process. Subsequently, VKORC1 re-cycles Vitamin K back to its reduced form.

Thus, loss-of-function mutations in GGCX and VKORC1 can result in rare heritable diseases ranging from coagulation factor deficiencies to PXE-like syndromes with multiple coagulation factor deficiencies.

Before the relationship between *ABCC6* and plasma PPI was known, it was hypothesized that deficiency of Vitamin K-dependent mineralization inhibitors is also a major factor in ectopic calcification in PXE (Vanakker et al., 2010; Boraldi et al., 2009). However, Vitamin K supplementation beyond normal nutrition fails to prevent ectopic calcification in a mouse model for PXE (Jiang et al., 2011; Gorgels et al., 2011; Brampton et al., 2011).

Nevertheless, warfarin – an inhibitor of VKORC1 – markedly accelerates ectopic mineralization in *Abcc6*^{-/-} mice (Li et al., 2013). Extrapolating from these pre-clinical data, Vitamin K antagonists should be avoided in patients.

8.2. Differential diagnoses of conditions with angioid streaks

AS can be present in a variety of retinal diseases. These include PXE, Paget's disease, and Sickle-cell disease.

Textbooks often provide the acronym 'PEPSI', but some of the implied associations of angioid streaks with Ehlers-Danlos syndrome is not validated and beta-thalassemia should be included.

8.2.1. Non-validated association with Ehlers-Danlos syndrome

Green et al. described two members from a family (mother and daughter) with Ehlers-Danlos syndrome with angioid streaks (Green et al., 1966). However, recent large-scale retrospective studies of Ehlers-Danlos syndrome revealed that none of 284 patients (Singman and Doyle, 2019), or only one to two of 227 patients (Mahroo and Hykin, 2019) showed angioid streaks.

Given the carrier frequency for pathogenic *ABCC6* variants and that carriers of monoallelic *ABCC6* mutations can show a mild retinal phenotype streak-like peripapillary changes (Gliem et al., 2020b), sporadic associations at rates of <1:200 should be dismissed in the absence of strong supporting evidence (e.g., genetic confirmation of the *ABCC6* status).

8.2.2. Beta thalassemia

Similar alterations to PXE have been described for beta-Thalassemia. In this genetic disorder, mutations affecting the beta-globin subunit of hemoglobin result in ineffective erythropoiesis and increased hemolysis, both leading to anemia. The genetic trait is most common in Mediterranean, subtropical, and tropical regions (Thomson et al., 2023).

AS, peau d'orange, pattern dystrophy-like changes, and optic disc drusen have been described for a large cohort. The prevalence of PXE-like alterations in a large cohort was 27.8% (70 of 255 patients). Further, vascular and dermatologic alterations similar to PXE can be found (A and V, 2009; Baccarani-Contri et al., 2001; Kurnia et al., 2021). Thalassemia intermedia are more severely affected compared to Thalassemia major patients. The underlying pathophysiology is hypothesized as a down-regulation of the *ABCC6* gene due to unknown processes, shown in a mouse model (Martin et al., 2011).

However, rare cases of co-inheritance of both diseases cannot be excluded (Boraldi et al., 2020).

8.2.3. Sickle cell disease

In the literature, angioid streaks are presented as a frequent finding in Sickle cell disease since the late 50ies, but the prevalence varies from 1% to 20%, with higher prevalence in older cohorts (Condon and Serjeant, 1976; Hamilton et al., 1981; Nagpal et al., 1976; Geeraets and Guerry, 1960a; Paton, 1959). PXE-like changes have been proposed to be limited to the eyes based on blinded skin biopsies (Hamilton et al., 1981; Nagpal et al., 1976), while other analyses found mild PXE-like changes in arterial walls and the dermis (Geeraets and Guerry, 1960b; Lippman et al., 1985). A histologic study of sickle cell disease retinae exhibiting PXE-like alterations has revealed marked calcification for BrM (Jampol et al., 1987).

PXE-like alterations in other hemoglobinopathies have been reported too, but in small numbers that need further validation (Kinsella and Mooney, 1988; Rodriguez et al., 1994; O et al., 1991). Also, angioid streaks are present in combinations of these hemoglobinopathies, such as 'sickle-thalassemia' (Goldberg et al., 1971; Aessopos et al., 1994).

8.2.4. Paget's disease

AS associated with Paget's disease has first thoroughly described by TL Terry in 1934, followed by case reports or case-series (Saito-Hakoda et al., 2023; Clarkson, 1991; Connor et al., 1961). Overall, the prevalence of angioid streaks in Paget's is estimated to be 6–8% (Connor et al., 1961; Terry, 1934).

8.3. Bruch's membrane diseases

Ester Grönblad already noted in her 1932 thesis that PXE and late AMD (referred to as Kuhn-Junius degeneration at the time) show a similar natural history in the late stages (Grönblad, 1932).

Recent data underscores that such similarities extend to even more diseases that can jointly be considered BrM diseases. Besides AMD and PXE, this group encompasses Sorsby Fundus Dystrophy, late-onset retinal degeneration.

All those diseases are characterized by.

- reticular pseudodrusen (Gliem et al., 2015a, 2015b; Cukras et al., 2016),
- early impairment of rod-mediated dark adaptation (Nigalye et al., 2022; Hess et al., 2020b; Steinmetz et al., 1992; Cideciyan et al., 1997; Jacobson et al., 2001; Owsley et al., 2007),
- acceleration of dark adaptation with Vitamin A supplementation (Hess et al., 2020b; Jacobson et al., 1995; Pfau et al., 2023),
- low signal in quantitative fundus autofluorescence (Gliem et al., 2016b, 2017),
- choroidal thinning and choriocapillaris loss (Hess et al., 2021b; Loewinger et al., 2023; Borrelli et al., 2017), and

- high risk of exudative neovascularization (Holz et al., 1994; Klein et al., 1999)

Malattia leventinese is frequently listed among those diseases too, but does not share all of the characteristics.

8.3.1. Sorsby Fundus Dystrophy (SFD)

First described by Arnold Sorsby, SFD is now known to be an autosomal-dominant disease due to a mutation in the *TIMP3*-gene (Sorsby and Mason, 1949; Weber et al., 1994a, 1994b).

The gene regulates the turnover of the extracellular matrix and is also a potent inhibitor of the vascular endothelial growth factor receptor 2, but the exact pathology is not yet fully understood (Jacobson et al., 2002; Alsaffar et al., 2022). Histopathologic and immunohistochemical studies revealed a high amount of misfolded TIMP3 protein in the sub-retinal deposits at the level of BrM (Alsaffar et al., 2022; Li et al., 2005).

A phenotypic overlap to PXE is given by the frequent presence of reticular pseudodrusen and the late stage of atrophy. Further, exudative CNV often results in anti-VEGF treatment in premature age (Raming et al., 2021; Sivaprasad et al., 2008). Of note, dark adaptation is subjectively and objectively impaired before any alterations can be found on multimodal imaging (Raming et al., 2021).

8.3.2. Late-onset retinal degeneration (L-ORD)

L-ORD is an autosomal-dominant disease due to mutations in the *C1QTNF/CTRP5* gene, mainly expressed in the RPE and ciliary epithelium (Ayyagari et al., 2005; Hayward et al., 2003).

More recent investigations showed a close connection of the gene to *HTRA1*, a risk gene for a specific AMD phenotype (Chekuri et al., 2019).

Histopathologically, sub-RPE deposits of lipids can be found, that spread from the central retina to the ora serrata. L-ORD patients exhibit phenotypic similarities to PXE and AMD, including reticular pseudodrusen, atrophy, while CNV is less frequent than in SFD (Borooah et al., 2009; Kuntz et al., 1996; Milam et al., 2000).

A feature characteristic for L-ORD is long anterior lens zonules, visible as very centrally inserting zonules on slit lamp examination (Ayyagari et al., 2005). Jacobson et al. have shown that dark adaptation dysfunction precedes morphological alterations (similar to SFD) and is therefore suitable to detect affected family members, if genetic testing is not available (Cukras et al., 2016; Jacobson et al., 2001).

8.3.3. Malattia leventinese (ML)

ML is an autosomal-dominant inherited disease, also known as Doyme-Honeycomb dystrophy or autosomal-dominant drusen. The causative gene is *EFEMP1*, which is expressed in the extracellular matrix (Gregory et al., 1996; Hé et al., 1996). The exact function is yet to be determined.

Histopathologically, sub-RPE deposition of altered EFEMP1 protein, TIMP3 protein and lipids could be found in mice. Similar to AMD, increased levels of complement factor C3 were found (Fu et al., 2007).

Funduscopically, confluent yellow drusenoid alterations can be found that often show a radial pattern. Due to the appearance of macular and peripapillary drusen in a reticular pattern, the term 'Honeycomb' was coined.

9. Treatment

There is no causal treatment for PXE available to date. The clinical care of patients is limited to the prevention and treatment of secondary complications. However, promising approaches are emerging and tested in phase 2 and 3 trials.

9.1. Prevention and treatment of complications

9.1.1. Eyes

Currently, the treatment of ocular alterations is limited to anti-VEGF

in the case of secondary neovascularization (also see Chapter 6 for details). Several agents have been proven efficient, however, many in studies including patients with angioid streaks, not confirmed PXE (Gliem et al., 2020a; Finger et al., 2008, 2011a; Lai et al., 2018). Treatment regimens include pro re nata, treat & extend and individual schemes. Compared to AMD, patients with secondary CNV due to PXE exhibit CNV about 25 years earlier, need more intensive treatment and are more often affected bilaterally (Raming et al., 2024).

9.1.2. Skin

While skin alterations are often the first alterations noticed by PXE patients, they are rather of cosmetic concern (Marconi et al., 2015). The alterations are often conceived as disfiguring, especially by women and desire for treatment is mostly given in patients with redundant skin at the neck.

For these, approaches such as surgical removal of skin sites, CO₂ laser and injection of collagen have been proposed (Salles et al., 2014; Galadari et al., 2003; Marwah et al., 2012; Viljoen et al., 1990; Akali and Sharpe, 2003; Ng et al., 1999). However, no clear evidence for these is given to date and intervention is normally not necessary.

9.1.3. Cardiovascular

In contrast to eye and skin alterations, cardiovascular involvement in PXE can be directly life-threatening or life-shortening. Treatment however is limited to prevention and targeting complications.

Prevention is paramount in these patients. Recommendations are similar to those for other causes of coronary artery disease, including a healthy lifestyle, a Mediterranean diet, quitting smoking, physical activity, and achieving a BMI of <25kg/m². Comorbidities such as arterial hypertension (goal: 130/80 mmHg max) and diabetes should be treated thoroughly since hypertension accelerates vessel calcification in a PXE mouse model (Omarjee et al., 2019b; Williams et al., 2018; Neumann et al., 2020).

Peripheral artery disease due to calcification of the femoral arteries (Fig. 8) occurs prematurely in PXE patients. However, due to the early onset and slow course of the disease, PAD is often well-compensated with extensive collaterals. Walking exercise should be recommended as a prevention and further support for collaterals by increasing muscle capillarization and angiogenesis (Kranenburg et al., 2017; McDermott et al., 2021; da Silva et al., 2022; Aboyans et al., 2018).

Interventional approaches, such as angioplasty and stenting for PAD

(i.e., the superficial femoral artery) in PXE have shown disappointing results (Ammi et al., 2015b).

Following atherosclerosis guidelines for the general population, all patients should be treated with lipid-lowering medication (i.e., statins) (Aboyans et al., 2018).

Additionally, multiple lines of pre-clinical evidence suggest that triglyceride and cholesterol dysregulation are contributors to vascular calcification in PXE (Brampton et al., 2021; Tiemann et al., 2020; Ibold et al., 2021; Guo et al., 2013).

Given the only study of statins in PXE was performed using atorvastatin and showed prevention of further arterial calcification in a mouse model, atorvastatin is favored over other compounds (Guo et al., 2013).

In line with high-risk non-PXE patients, Low Density Lipoprotein (LDL) levels in PXE should be kept within very tight limits (Cosentino et al., 2020).

Anticoagulation has been used with caution in the past due to a hypothesized increased risk of retinal hemorrhages. But in AMD as a much more common disease, there is no evidence substantiating a causal link between anticoagulation and risk of retinal hemorrhages (Ying et al., 2016; Buitendijk et al., 2018). A large prospective trial on this matter is still ongoing (Robman et al., 2017, 2020).

9.2. Previous and future therapeutic approaches

The current focus of treatment development for PXE is on pyrophosphate augmentation in different ways. Currently in a Phase III trial is the direct pyrophosphate augmentation ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04868578) identifier NCT04868578) as well as pyrophosphate analogue etidronate (NCT05832580).

Related approaches include the infusion of a recombinant ENPP1-Fc protein to increase pyrophosphate generation (NCT05030831), and TNAP-inhibition to reduce pyrophosphate hydrolyzation (NCT05569252).

Previously, other inhibitors of ectopic mineralization, such as magnesium (NCT01525875), have been evaluated. Interestingly, previous phase 2 trials showed promising results but phase 3 failed. A possible explanation are the outcome measures chosen for the clinical trials. Skin alterations (as biopsies for the Magnesium study) and vascular imaging markers (as femoral ¹⁸fluoride sodium positron emission tomography activity used for the Etidronate study) might be affected too late in the disease course and/or carry a high interindividual heterogeneity.

In a study objectifying dark adaptation alterations in PXE, two patients were administered 15'000 IU of Vitamin A orally and both showed an improvement of dark adaptation within 4 weeks (Hess et al., 2020b).

Ocular alterations have not yet been used as outcome measures for clinical trials but might be beneficial due to its non-invasive imageable tissue and clinically visible progression over the patients' lifetime. To target this issue, the ProPXE study currently prospectively assesses and compares ocular outcome measures over a time period of 2 years (NCT05662085).

10. Treatment and Monitoring suggestions for ocular alterations in PXE

Based on clinical and scientific knowledge, we suggest the following for the ophthalmologic PXE clinic.

- Advise for performing a cardiovascular check-up at the time of diagnosis and follow the experts treatment and monitor regimens
- Advise for refraining from contact sports and/or to wear protective glasses, due to the risk of retinal bleedings after trauma
- Perform annual ocular follow-up for non-neovascular eyes
- Inform about the high-risk of CNV development
- Treatment of exudative neovascularization with anti-VEGF injections, a close treat & extend regimen appears favorable

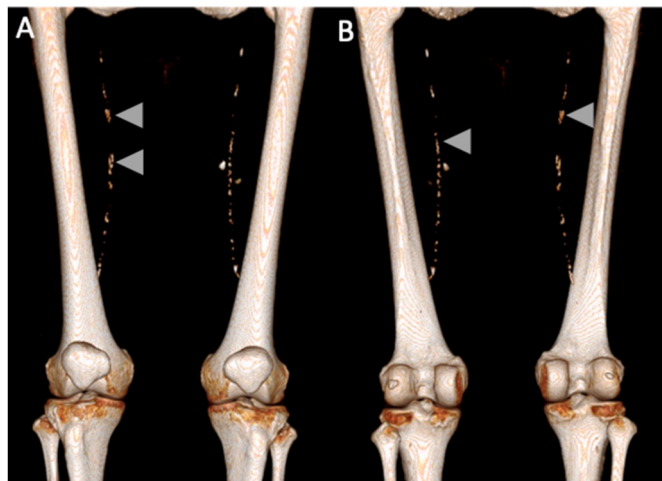


Fig. 8. Vascular calcification in Pseudoxanthoma elasticum
Non-contrast computer tomography (CT) scan with 3D reconstruction of the femoral area shows multiple lesions of calcification within the femoral artery. Due to the slow course of the disease, collaterals compensate the restrictions resulting in delayed symptoms in patients with PXE. Vascular imaging often shows widespread alterations in only mildly affected patients.

- Take into account RPE dysfunction in case of non-resolving sub-retinal fluid with treatment
- Close examination of the fellow eye should be performed when anti-VEGF treatment started in the first eye
- No treatment of non-exudative neovascularization

11. Summary and future directions

Pseudoxanthoma elasticum is an inherited multisystemic disease, leading to calcification of elastic fibers. Ocular consequences arise from calcification of BrM, in which elastic fibers are abundant. Characteristics of PXE include AS, peau d'orange and comet (tail) lesions. Cardiovascular involvement leads to atherosclerosis and reduced walking distance, as well as to life-threatening complications including thromboembolic events. Skin alterations can be guiding when diagnosing the disease, but otherwise are rather of cosmetic concern.

Much has been discovered in the last 10 years in PXE research, however, the exact disease mechanism still needs to be discovered. Also, the subfields of ocular, vascular and dermatologic PXE research have explored the field individually, making now a joint approach a pressing need to explore the whole spectrum and multisystemic interplay of the disease.

To date, no causal treatment is available, but promising approaches – targeting the lower pyrophosphate levels in PXE – are currently tested in phase 2 and 3 trials. Several propitious approaches have failed in the past, possibly due to insensitive endpoints. Here, ocular alterations could be an aspirant, due to its spatial progressing and novel imaging techniques for non-invasive imaging and precise quantification of these lesions.

CRediT authorship contribution statement

Kristina Pfau: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Imre Lengyel:** Writing – review & editing, Visualization. **Jeannette Ossewaarde-van Norel:** Writing – review & editing, Visualization. **Redmer van Leeuwen:** Writing – review & editing, Visualization. **Sara Risseuw:** Writing – review & editing, Visualization. **Georges Leftheriotis:** Writing – review & editing, Visualization. **Hendrik P.N. Scholl:** Writing – review & editing. **Nicolas Feltgen:** Writing – review & editing. **Frank G. Holz:** Writing – review & editing, Resources. **Maximilian Pfau:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Data availability

No data was used for the research described in the article.

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