PXE and Your Eyes

What Is PXE?

Pseudoxanthoma elasticum, (PXE), is an inherited disorder that causes some tissue in the body to become mineralized, that is, calcium and other minerals are deposited in the tissue. This can result in changes in the skin, eyes, cardiovascular system and gastrointestinal system. PXE was recognized over a hundred years ago. A number of significant advances have been made in the past few decades.

What Are the Effects of PXE?

PXE results in a variety of signs and symptoms. The number, type, and severity of signs of PXE are different for each person. Certain effects of PXE can cause serious medical problems while others have less impact. The effects of PXE may include: skin changes; changes in the retina of the eye that may result in significant loss of central vision; changes in the cardiovascular system that may involve calcification of arteries and decreased blood flow in the arms and legs; changes in the gastrointestinal system that may lead to bleeding in the stomach or intestines.

The Eye

One of the organs affected by pseudoxanthoma elasticum (PXE) is the eye. In particular, the retina is the part of the eye most affected by PXE. Symptoms of PXE in the eye tend to evolve in stages. Initially patients may develop peau d'orange, or a discoloration of the fundus. As symptoms progress, the retina may develop angioid streaks, or breaks in the Bruch's membrane caused by the mineralization of this elastin rich layer. Neither of these symptoms alone will cause vision loss, but the breaks in the Bruch's membrane allow choroidal neovascularization (CNV), or unwanted growth of abnormal and fragile blood vessels up through the cracks in the membrane. These blood vessels may leak, and in doing so, disrupt the structure of the retina and decrease central vision. However, like all PXE symptoms, severity varies widely. While some patients may eventually become legally blind due to the loss of their central vision, others may only experience benign eye symptoms with no vision loss at all. This bulletin is designed to explain in depth the eye symptoms experienced by patients with PXE, their typical progression, and the effectiveness of available treatment options.

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PO Box 189 • Damascus, MD 20872 • 202.362.9599
sterry@pxe.org • pxe.org

The Retina

The eye is built very much like a camera. Light comes in through the pupil. Behind the pupil, there is a lens that focuses light to the back of the eye, where it falls on the retina. The retina detects light and sends information to the brain, so that you can make sense out of it. The retina is composed of four parts: the optic nerve, the retinal blood vessels, the macula, and the periphery. The optic nerve is responsible for carrying the information from the eye to the brain. The retinal blood vessels supply circulation and nutrients to the retina itself. The macula is responsible for central vision, and the periphery is responsible for peripheral vision. Changes in the macula are responsible for most of the vision loss in PXE. These macular changes result in a loss of central vision, which is used during tasks such as recognizing faces or looking at fine print.

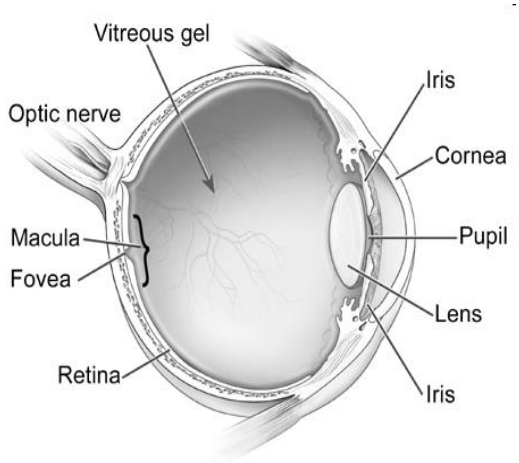

Figure 1 – Structure of the eye

The retina is a very thin, transparent, and fragile layer of nerve cells and light receptors. In fact, the retina is only 1/5 of a millimeter thick. The retina rests on a layer of cells called the retinal pigmented epithelium (RPE), which in turns rests on a very thin elastic layer called Bruch's membrane. Beneath Bruch's membrane is a system of small choroidal blood vessels that supply the retina with nutrients and oxygen and take away waste products.

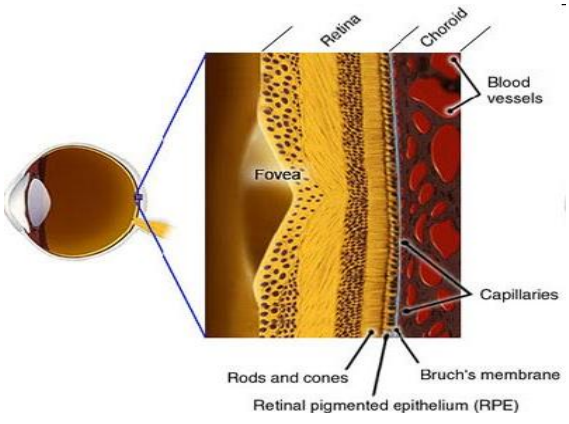

Figure 2 – Structure of the retina

Early Retinal Changes in PXE

<u>Peau d'orange</u>

Many early changes in the retina in PXE are helpful in diagnosing the disease but may not cause problems to patients. One such change is called peau d'orange, a French word meaning orange peel. With peau d'orange, some areas of the retina appear spotted and yellow. When seen at some distance, it looks like the skin of an orange, for which it is named. There is no negative consequence from having peau d'orange, but it does help diagnose PXE in a patient. Peau d'orange can be seen in early childhood and usually comes before the development of angioid streaks.

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Angioid Streaks

One of the most characteristic changes in the retina as a result of PXE is angioid streaks. Angioid streaks are cracks in Bruch's membrane, the thin elastic layer under the retina and the RPE. Angioid means like blood vessels, and the condition is so named because the breaks in Bruch's membrane look like blood vessels when the retina is examined (see Figure 3). The overlying retina in the early stages is quite normal.

Angioid streaks can develop in PXE as early as the teenage years and tend to accumulate with time. A retinologist looks for angioid streaks during an examination using imaging studies. One such imaging tool is fluorescein angiography, which uses a special dye to assess blood flow in the retina. Another is optical coherence tomography (OCT), which uses wavelengths of light to come up with an image of the retina. Angioid streaks form in PXE because of abnormal elastic fibers in Bruch's membrane that tend to calcify and make it more brittle and prone to cracking and breaking. When Bruch's membrane cracks or breaks, the overlying retina may become damaged or atrophied and less functional in the area around the crack, or angioid streak. In addition, small capillaries in the choroid can grow through these cracks and leak or bleed.

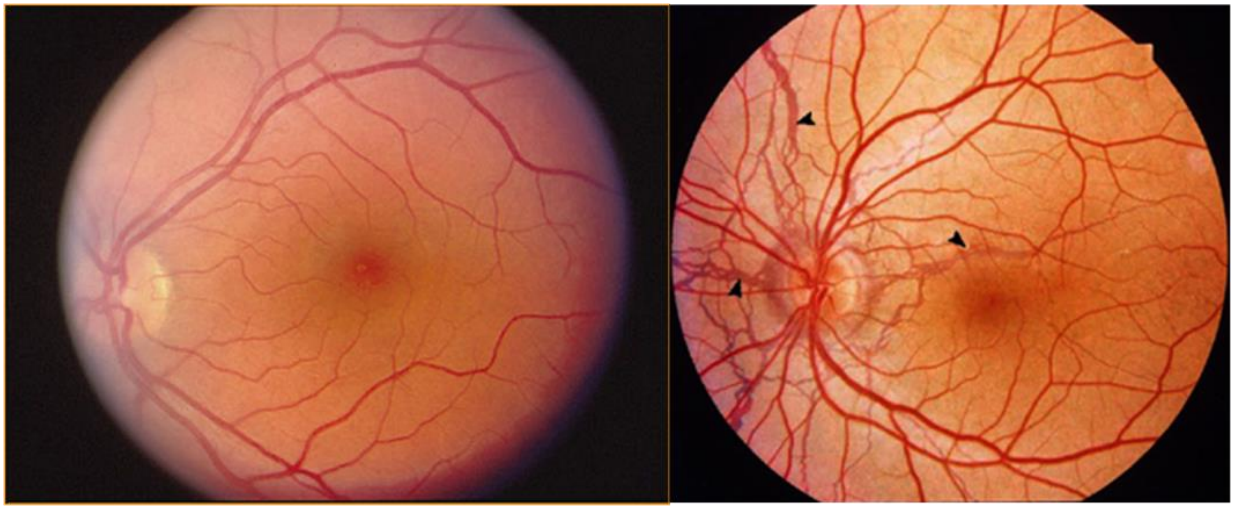

Figure 3 – Left: normal retina; Right: retina with angioid streaks (indicated by small arrowheads) in Bruch's membrane

There is presently no known treatment to prevent the formation of angioid streaks. Prevention methods that can reduce the amount of damage done to the eye include avoiding eye trauma and wearing eye protection for sports. When angioid streaks have formed or are starting to form, retinologists suggest regular retinal exams to watch for retinal bleeds. Individuals should check themselves regularly using the Amsler grid. This checkerboard-like grid allows a patient to notice minor changes in vision that can signal the presence of bleeding or leakage occurring in the retina. An Amsler grid with instructions for using it can be found at http://pxe.org/amsler-grid.

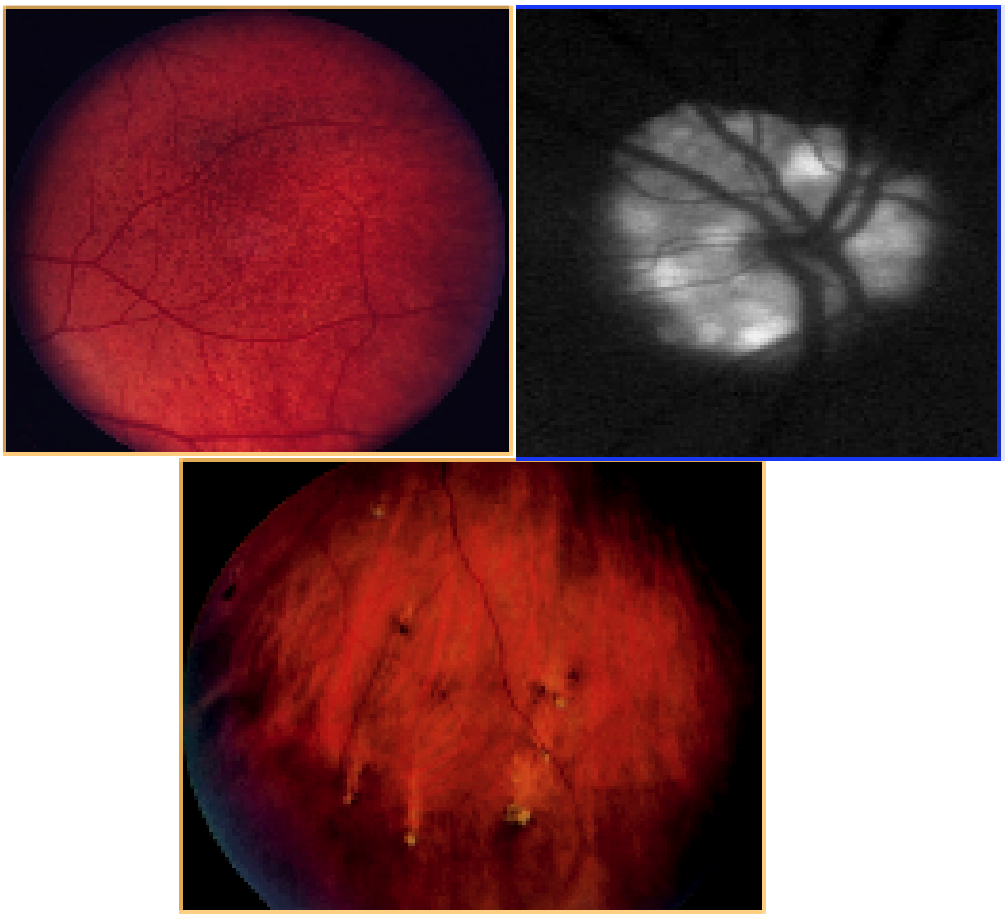

Figure 4 – Top left: Peau d'orange. Top right: Optic Drusen. Bottom: Comet Lesions (arrow)

Drusen and Comet Lesions

Drusen, a general term literally translated as stones, are tiny yellow or white accumulations of material under the retina. Drusen are not a specific finding in PXE - people with and without PXE may have them. Two types of drusen occur in PXE - optic nerve drusen and comet lesions. Optic nerve drusen are rare in PXE and are not usually associated with any symptoms. They appear as lumps around the optic nerve, as seen in Figure 4. Comet lesions have yellow or white bodies and a tapered tail, like a comet, as seen in Fig 4, right panel. They are usually found in the periphery of the retina in patients with PXE. While angioid streaks and optic nerve drusen can occur in other diseases, comet lesions occur only in PXE, and represent another early change of the retina in PXE. Thus, comet lesions are helpful for diagnosing PXE based on an eye examination, especially if seen with angioid streaks. People diagnosed with age-related macular degeneration (AMD) are also described as having drusen, however, despite the common term, the drusen associated with PXE are different from those associated with AMD.

Late Retinal Changes in PXE

Many patients experience vision loss during the late retinal changes in PXE. This loss of vision usually results from choroidal neovascularization (CNV). CNV is the growth of new blood vessels from the choroid, the layer of blood vessels underneath Bruch's membrane. This growth occurs through the cracks in Bruch's membrane where the angioid streaks are located. These vessels are abnormal and can leak blood and plasma into the space underneath the RPE, distorting and elevating the retina like a blister and distorting vision. CNV also disrupts the structure of the retina and can lead to scarring of the retina. Retinal scarring and changes in the retinal structure caused by CNV can cause a patient to experience permanent central vision loss, especially if these problems occur in the macula.

Symptoms of CNV include acute distortion of central vision and reduction in visual acuity. Patients may have difficulty reading print, may see a central dark spot in their vision, or experience distortions in central vision. Distortions in central vision can be detected using the Amsler grid. A normal eye will see all the lines as being straight (Figure 5).

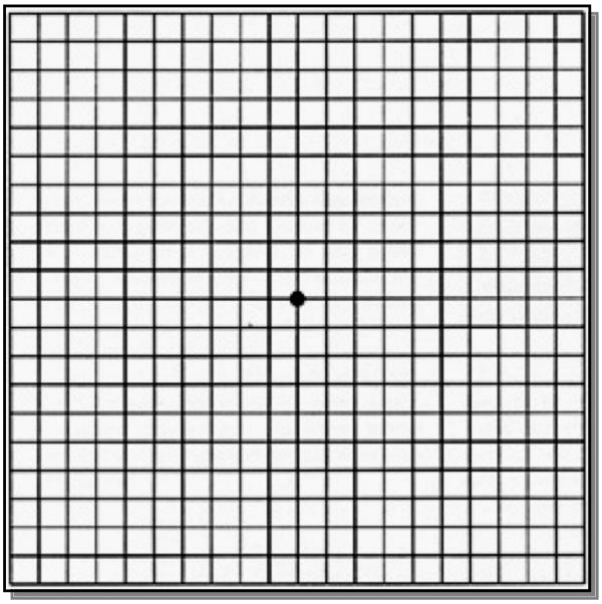

Figure 5: Normal view of the Amsler Grid

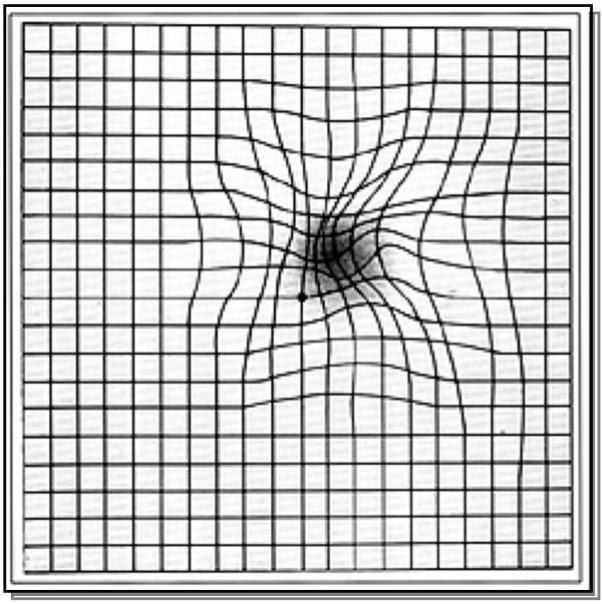

Figure 6: An eye with CNV and leaking might see the pattern as being distorted or uneven, or with a dark spot on the grid (Figure 6).

Treatment Options for Eye Changes in PXE

Although there is no treatment to prevent CNV, there are a number of treatments that can reduce the amount of damage done by CNV. Almost all the treatments used in PXE were developed for the treatment of wet age-related macular degeneration (AMD), another disease of the retina. Similar CNV and leakage, bleeding and scarring can occur in AMD, but the mechanisms are different. PXE is so uncommon in comparison to AMD that there have not been enough patients to conduct controlled clinical trials of these treatments in PXE.

In the past, photocoagulation, also known as hot laser, was used. This technique burns away the abnormal new blood vessels of CNV that form in the retina. One problem with this technique is that it destroys normal tissue along with the unwanted blood vessels, and the damage to the surrounding retina causes scarring and permanent vision changes. The major problem with hot laser therapy is that CNV and bleeding tend to recur after treatment, inevitably leading to more bleeding and scarring.

To address this issue, photodynamic therapy (PDT), also known as cold laser, was developed. PDT involves an injection of a chemical into the bloodstream that concentrates in the new blood vessels in the retina and is activated by the wavelength of a cold laser. The energy released by the activation can help seal the blood vessels without producing a lot of damage to the surrounding retina. Unfortunately, although safer than hot laser, there are also recurrences of CNV, leaking and bleeding in patients with PXE after PDT. Neither of these is used any more.

Most recently, anti-angiogenic or anti-VEGF treatments, such as Avastin® (bevacizumab), Lucentis® (ranibizumab), and Eyelea® (aflibercept) have been developed. VEGF, an acronym for vascular endothelial growth factor, is an important growth factor that CNV relies on to grow and develop. These medications are specific antibodies to these growth factors which when injected into the eye, can bind up VEGF and help control the leakage and growth of CNV. Significant improvements in visual acuity can be achieved in patients with PXE with the use of anti-angiogenic (anti-VEGF) agents. In fact, the anti-angiogenic agents have been sufficiently effective to have largely replaced the previously used methods of treatment such as laser photocoagulation and photodynamic therapy. A recent clinical trial compared Lucentis® to Avastin® for the treatment of CNV in AMD and found them to be equally effective in a number of different ways. Although the trials did not include patients with PXE, it is possible that the results can be extrapolated to PXE, and that these two medications also appear to be effective for treatment of CNV in PXE.

Treatment for long-standing vision loss is rather difficult. Retinal scarring and cell loss within the retina are usually permanent. Perhaps in the future it will be possible to regenerate retinal cells that are damaged through stem cells, but this is not yet practical. Low vision aids and rehabilitation are recommended when vision loss is disabling and permanent. For many patients, low vision aids and magnifying computer software can be very helpful in overcoming the restrictions imposed by central vision loss.

What Can You Do to Protect Your Eyes?

Patients with PXE should see an ophthalmologist regularly. The ophthalmologist will dilate the pupils to look for peau d'orange and angioid streaks. Most patients with angioid streaks are followed by a retinal specialist because they are best trained to use anti-angiogenic treatments. Retinologists also suggest that people with PXE not engage in activities that might cause direct eye injury, such as football, boxing, heavy weightlifting or deep-sea diving. Wearing protective eyewear during sports is also highly recommended. Aerobic exercise, and other sports and activities for which direct trauma or pressure on ocular structures is not a factor, may be usually pursued by patients with PXE without causing ocular side effects.

Fortunately, the effects of PXE on the various organ systems of the body are similar to those produced by much more common conditions – so you need to find a doctor who is caring and listens and takes the time to become educated about PXE. He or she can read our medical bulletins and learn how to care for you. He or she can also consult us (we have gathered data on more than 1000 affected individuals) if necessary.

Key Facts:

- The eyes are one of the **most affected organs**
- There are a number of signs that the eyes are affected including **peau d'orange, angioid streaks**, and sometimes retinal bleeding.
- Looking at the **Amsler grid** each day can help give you an early warning of a bleed.
- **Antiangiogenesis** injections are very helpful in stopping bleeding in the retina and should be done as soon as you notice a bleed.