

PXE General Bulletin



INTERNATIONAL

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What Is PXE?

Pseudoxanthoma elasticum, PXE, is an inherited disorder that causes select elastic 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 years.

How Rare Is PXE?

Estimates of the incidence of PXE range from 1 in 100,000 people to 1 in 25,000 people. However, the true incidence of PXE is not known in any population. It is possible that some individuals affected by PXE are not yet diagnosed (and may never be), particularly people with mild signs of PXE, or those whose signs are not typical.

What Are the Signs that Lead to Diagnosis?

Changes in the skin are usually the earliest sign of PXE, and lead to the definitive diagnosis. Although the signs of PXE and the age of onset vary considerably, many people first notice an unusual appearance of their skin, usually on the sides or back of the neck. Small bumps or lesions, called papules, may appear. These have been described as looking like a rash or like an unwashed neck. Usually a small biopsy of a lesion is taken to confirm the diagnosis of PXE.

The biopsy requires a very small piece of skin, the size of a pencil eraser, be taken from the neck, underarm and/or inside the elbow. The biopsy is sent to a laboratory where a special stain, the von Kossa stain, is used to detect calcium in the tissue.

For other people, changes in the eye are the first noticeable sign of PXE. Early changes in the eye are visible only during an ophthalmologic examination. Later symptoms can include loss of central vision. Some people are first diagnosed with PXE when they notice distortion of their vision.

What Are the Effects of PXE?

PXE results in a variety of signs and symptoms. The number, type, and severity of signs of PXE vary from person to 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 or even the heart and brain; changes in the gastrointestinal system that may lead to bleeding in the stomach or intestines.

At present, there is no way to predict the progression of the disorder for a particular individual. Some people have no skin lesions; others have no vision loss. Many people do not experience gastrointestinal complications or

cardiovascular difficulties. And a few have no manifestations of PXE except for a positive skin biopsy or angioid streaks. The effects of PXE and its rate of progression seem to have no discernable pattern. Thus there is great variability in how PXE affects each person.

Skin

PXE often causes visible changes in the skin. These changes vary from person to person. The earliest changes are usually in the skin on the sides of one's neck. Small lesions called papules may develop (see Figure 1).



Figure 1

They may resemble a rash or have a "cobblestone" appearance. These lesions in the skin can progress slowly and unpredictably, from the neck downward. With time, the lesions can come together to form plaques, and the skin becomes loose and wrinkly (see Figure 2). Skin signs of PXE can occur in young children. The areas of the body that are most affected are those which bend and flex. The neck, the underarms, the skin on the inside of the elbows, the groin, and the skin behind the knees may be progressively affected, leading to loose folds in these areas. Some of these changes may be alleviated by reconstructive or

plastic surgery. Lesions may also appear on mucous membranes such as the inside of the lower lip or lining of the rectum or vagina but cause no symptoms or cosmetic abnormality.

It is possible to have PXE and not have any apparent skin lesions. In some individuals, careful examination of the skin by a dermatologist does not reveal any visible lesions, but a positive biopsy indicates the diagnosis of PXE.

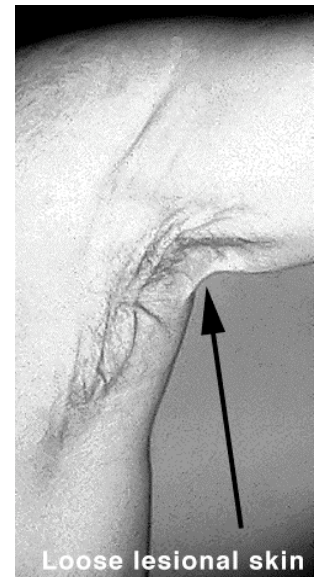


Figure 2

Eyes

PXE affects the retina of the eye. The first change, visible only during an ophthalmologic examination with dilated pupils, is a mottled texture that is called peau d'orange (literally "skin of an orange" in French) because the retina looks like the surface of an orange peel. Peau d'orange usually appears in childhood or early adolescence.

Characteristic irregular streaks, called angioid streaks (see Figure 3), almost always develop,

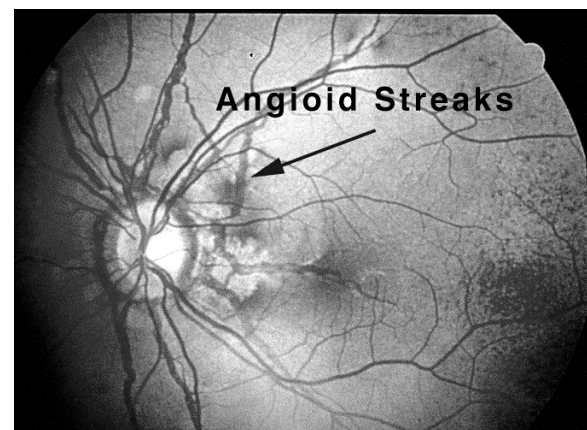


Figure 3

sometimes even in childhood. Angioid streaks are cracks in the highly elastic membrane behind the retina (Bruch's membrane). Neither peau d'orange nor angioid streaks affect the vision. Both appear before vision loss is noticed. However, small blood vessels beneath this layer can take advantage of the breaks in the membrane and grow through the membrane. This is called subretinal choroidal neovascularization (CNV). Sometimes these blood vessels leak and bleed. This bleeding results in distortion and loss of central vision. While people with PXE may lose so much central vision that they become legally blind, almost all people with PXE continue to have peripheral vision.

A person with PXE can use a self-diagnostic tool, called an Amsler grid, to monitor central vision. If there is swelling or bleeding in the center of the retina, this may cause the intersecting lines of the Amsler grid to appear distorted. A retinal specialist can instruct a patient in the use of an Amsler grid. The retinal specialist should be consulted immediately when distortion on the Amsler grid is noticed.

Some current treatments used for macular degeneration, especially the intraocular injection of anti-angiogenesis drugs such as Lucentis™ and Avastin™, appear to also be effective in PXE. In the past, laser treatment to control retinal hemorrhage was often used. In most cases, scarring from both the bleeding and the laser surgery has made vision worse.

A variety of aids, including optical, non-optical, and electronic, can help maximize remaining vision and allow the person with low vision to maintain independence. A low vision optometrist can evaluate low vision acuity using specialized tools and charts, and low vision rehabilitation services can prescribe devices specific to your needs. PXE International can help find low vision services in your area.

People affected by PXE should avoid activities

that might cause direct trauma to the eyes, such as contact sports, as these may encourage retinal bleeding. Activities that increase pressure in the eyes, such as weight lifting, scuba diving and the Valsalva maneuver, should also be avoided.

Cardiovascular System

PXE frequently causes mineralization in the elastic layers of medium-sized arteries. This causes narrowing of blood vessels, so affected individuals may have decreased blood flow to the arms and legs. Decreased flow of blood to the arms and legs may mean that one's pulse can no longer be felt in the wrists or feet. This decreased flow of blood to the arms and legs may also cause cramping or pain in the legs or arms when walking or exercising. This cramping is called intermittent claudication.

Arterial narrowing and reduced blood flow can also cause angina (chest pain), heart attack, small strokes and intestinal angina (abdominal pain).

It is thought that hypertension (high blood pressure) is more common among people with PXE than in the general population, but no large study has been done to substantiate this. Hypertension should be aggressively treated to reduce the risk of heart attack and stroke.

It has been reported that mitral valve prolapse occurs more frequently in people with PXE than in the general population. These reports, however, have not been substantiated in large studies.

Individuals with PXE should have periodic visits to their physician for monitoring of blood pressure, cholesterol, and pulses in the arms and legs. A heart-healthy lifestyle is recommended, with low fat foods and plenty of exercise. Consistent exercise may decrease the effects of PXE on the blood vessels. Maintaining normal weight may also be beneficial. Smoking should be avoided.

Gastrointestinal System

Very rarely, PXE may cause acute upper gastrointestinal bleeding. This is sometimes not recognized immediately and can be life-threatening. It can present with vomiting of blood or passing black, tarry stools. There is not much known about the actual cause of this bleeding except that the bleeding can occur from multiple points in the stomach and/or intestines. In a few cases it is mistaken for bleeding ulcers. A person with PXE experiencing any gastrointestinal difficulty should be sure to tell their physician that they have PXE. Affected individuals should not take non-steroidal anti-inflammatory medications, such as aspirin, ibuprofen and naproxen, because they increase the risk of gastrointestinal bleeding by causing superficial erosions in the stomach.

Pregnancy

A study of 795 pregnancies of 306 women with PXE has shown that most women with PXE have a normal pregnancy, labor, delivery, and post-partum period and can nurse normally. The incidence of upper gastrointestinal bleeding during pregnancy in PXE is less than 1%, much less than previously reported in smaller studies. The fetus is not adversely affected by its mother having PXE. In addition, having been pregnant in the past does not affect the ultimate severity of skin, eye, or cardiovascular manifestations of PXE in women over 40.

Breast and Testicular Calcifications

A study of mammograms of women with PXE has shown that women with PXE have microcalcifications in their breast tissue, and that the majority of the microcalcifications are benign – they are not a sign of breast cancer. This is important because radiologists diagnose breast cancers on mammograms by the way microcalcifications cluster. However, the signs of breast cancer on mammography are the same

for women with PXE so it would therefore be wise to inform the radiologist of the diagnosis of PXE at the time the mammogram is done.

A study of testicular ultrasound in men with PXE has shown that multiple bilateral calcifications in testicles appear to be common, and are generally not associated with cancer. This is important because testicular cancers are diagnosed on ultrasound as clusters of small calcifications. However, men with PXE have the same risk of testicular cancer as the general population and the radiologist should be informed of the diagnosis to help in interpreting the findings. Incidental small calcifications have been found in the spleen and kidney on abdominal ultrasounds. These are usually a marker for PXE and probably of no significance. The radiologist should therefore be informed of the diagnosis in order to assess the significance of these findings.

What Kind of Medical Care Will Be Needed?

Initially, a newly diagnosed individual should have assessments by a primary care physician, ophthalmologist, dermatologist, and cardiologist. People affected by PXE must find healthcare professionals who are willing to learn about PXE, since there will be few well-informed professionals. Gene Reviews has a thorough clinical description for the healthcare provider and would be a good piece of information to print and bring to the healthcare provider (<http://www.geneclinics.org/profiles/pxe>). PXE International has bulletins available online for the ophthalmologist, dermatologist, primary care physician, pediatrician, obstetrician and dentist (www.pxe.org).

Regular physical exams by a primary care physician are recommended. A detailed family history should be taken with regard to onset, signs that may be related to PXE and the rest of the family's medical history. The affected

individual's blood pressure and cholesterol and triglycerides should be monitored and abnormalities aggressively managed. Peripheral pulses should be monitored as well. A dermatologist will most likely be the physician to make the definitive diagnosis and can also offer advice on reconstructive surgery if that is of interest to the patient. A cardiologist should perform a baseline EKG, cardiac stress test, echocardiogram, and Doppler evaluation of peripheral arteries. An ophthalmologist will dilate the eyes to look for peau d'orange and angioid streaks. If angioid streaks are found, it is wise to consult a retinal specialist.

Will Other Family Members Be Affected?

PXE is inherited as an autosomal recessive disorder. This means that both copies of the gene for PXE must be altered or changed in order for a person to have signs and symptoms of PXE. A person with one altered gene is called a carrier. Having only one altered or mutated gene does not make much of a difference clinically and the carrier doesn't usually have PXE since the working gene still performs its function. A person inherits PXE when both parents are carriers of the altered gene associated with PXE and have both passed it on to the offspring.

Although PXE is autosomal recessive, some families have more than one generation of people with PXE. This might happen because of pseudodominance. This happens when an affected individual with two altered or mutated PXE genes mates with a carrier who has one PXE mutation (and looks outwardly normal with no signs of PXE). With each pregnancy there is a 50% chance of having an affected child. This is more common when there is a high carrier frequency.

What is important to note, however, is that while there are a few families with two generations of people with PXE, there have not

been any families found with three or more generations of people with PXE. This makes it highly unlikely that there is an autosomal dominant form of PXE, which would require only one changed copy of the gene associated with PXE to cause symptoms.

It is important to look carefully at the siblings of a newly diagnosed individual. Either a genetic test or a skin biopsy can be used to definitively diagnose PXE.

What Research Is Being Conducted on PXE?

This is an exciting time for PXE research. The gene associated with PXE has been identified and a genetic test for PXE is available.

Other PXE research projects include clinical studies: determining what characterizes PXE, how it progresses, and what changes it causes in various systems of the body. In addition, much exciting research at the cellular and molecular level is giving us insights into how the PXE gene works in the body. There is even an animal (mouse) model of PXE that will enable us to study potential treatments for PXE. And perhaps in the coming years we will see a treatment for PXE. All that is needed is funding - scientists are ready to do the work necessary.

Retinal research is advancing quickly. There are many projects looking at angioid streaks, retinal bleeding and what can be used to alleviate the bleeding and loss of vision that often follows.

Where Can My Doctor or I Get More Information?

PXE International publishes informational bulletins for affected individuals and for physicians, including separate bulletins about PXE's effects on the eyes and the skin, during pregnancy, in children, and for pediatricians and dentists. PXE International publishes a

newsletter in which current research projects and findings are announced and news is shared about local support groups of PXE International. These are all available by mail or online at the PXE International website. PXE International manages a blood and tissue bank, which is vital for research on PXE. In addition, PXE International initiates and funds research projects.

Can You Recommend a Doctor Who Knows PXE Well?

We cannot recommend a doctor who is familiar with PXE, unless you are looking for an ophthalmologist or dermatologist.

Since there are over 7000 rare diseases, doctors cannot be familiar with all of these diseases. Furthermore, you might find a general practitioner or cardiologist who has seen a PXE patient or two, but every person is different and you would not want a doctor to base your care on the few other cases he or she has seen.

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 over 600 affected individuals) if necessary.

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