

Vascular Manifestations of PXE

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Pseudoxanthoma Elasticum (PXE) is a genetic disorder that affects connective tissue and leads to the progressive mineralization and fragmentation of elastin fibers. It predominantly affects the skin, eyes, and vascular system. If you have PXE, it is important that you follow a lifestyle that can protect your vascular health. It is also essential that you and your doctor are aware of the signs and symptoms of vascular disease in PXE.

What is Vascular Disease?

The heart pumps blood through a system of blood vessels called the circulatory or vascular system. Arteries carry blood away from the heart and veins return blood back to the heart. These vessels are elastic tubes that carry blood to every part of the body. Vascular disease includes any condition that affects your circulatory system. When arteries become narrowed, oxygenated blood cannot reach certain areas of the body. The lack of oxygen can cause pain and/or cell death. Thus, the signs and symptoms of vascular disease are determined by the part of the body being affected by reduced blood flow. For example, a blockage in the arteries of the heart can cause a heart attack while narrowing of the arteries in the leg can lead to pain in the calf with exercise.

When plaque forms in the walls of arteries (a process called **atherosclerosis**, literally hardening of arteries due to fatty plaques), the inside of the artery through which blood flows becomes narrowed. Plaques are made up of smooth muscle cells, inflammatory cells, lipids, cholesterol, calcium, and a fibrous cap. Because there are arteries throughout your body, atherosclerosis is a systemic disease that affects the whole body and is associated with high rates of cardiovascular morbidity and mortality. In PXE, the process of blood vessel narrowing is somewhat different than in atherosclerosis, but the end result is the same, namely the narrowing of arteries.

In PXE, vascular disease may occur prematurely. It involves calcification of the elastic layer of blood vessels and narrowing of blood vessels. Calcification in blood vessels is seen not only in patients with PXE, but also in patients with diabetes, heart disease, and advanced age. In PXE, calcification usually occurs in the elastic layer of small to medium sized arteries. The mechanism of the mineralization of blood vessels is unclear, but it is thought to be caused by injury to the inner lining of blood vessels and a chronic systemic inflammatory state that is created.

Peripheral Arterial Disease

The most common vascular manifestation in PXE is **peripheral arterial disease (PAD)**. PAD is caused by narrowed arteries which reduce blood flow to the extremities, usually the legs. In PAD, the limbs do not receive enough blood flow to keep up with the demand. The most common symptom of PAD in PXE is leg pain when walking, which is called **intermittent claudication**. It has been reported as early as age six, but it usually occurs after the fourth decade of life. Intermittent claudication rarely progresses to critical limb **ischemia** (insufficient blood flow or oxygenation) or limb loss. Signs of critical limb ischemia include pain at rest or a wound on the foot that does not heal due to lack of blood flow. **Rest pain** is severe pain in the front of the foot that occurs even without exercise due to lack of blood flow at rest. It usually occurs at night. Dangling the foot off the bed so gravity can help get blood flow to the toes can alleviate rest pain. It is important for you and your doctor to distinguish rest pain from leg or foot cramps, diabetic neuropathy, or restless

leg syndrome. Physical exam with attention to vascular health and vascular studies can help.

Diagnostic Testing for PAD

Signs of PAD on physical exam include diminished or absent pulses in the legs or feet, loss of leg hair, thickened nails, pale cool skin, or a reddish color to the toes. This reddish discoloration is known as **dependant rubor** because it occurs when the feet are dangling down or the individual is standing. Diagnostic testing for PAD includes invasive and non-invasive imaging studies.

Non-invasive – Ankle brachial indices (ABIs) and ultrasound (Doppler tests) are non-invasive studies that are very helpful in diagnosing, determining severity of and following vascular disease. Ankle brachial indices compare the blood pressure in your ankle to the blood pressure in your arm. In this test, you may be asked to walk on a treadmill and have readings taken before and after exercising to capture the severity of the narrowed arteries during walking. Ultrasound can evaluate blood flow through blood vessels and identify arteries that are narrowed or blocked. It is these non-invasive studies that are typically required to diagnose and follow blockages in patients with vascular disease.

Invasive – Computerized tomographic (CT) angiography, magnetic resonance angiogram (MRA) and arteriograms are more invasive because they require a needle stick and dye to be injected into the blood vessels in order to demonstrate blockages. Arteriograms allow the surgeon to see the blood flow as it happens and to perform balloon angioplasty and stenting if indicated. More invasive testing should only be performed if an intervention or treatment is needed.

Treatment for PAD

Exercise – An exercise regimen is the cornerstone of therapy for relief of symptoms of intermittent claudication. An exercise regimen includes walking for around 30-45 minutes three to four times a week. Walk until moderate claudication pain is reached, and then rest until symptoms subside. After the pain subsides, continue walking and rest again when you feel pain. The goal is to increase the distances you are able to walk over time before you feel pain. The pain that you feel when you exercise is not causing harm, but actually telling the body to grow blood vessels around the blockages. An exercise regimen can improve function and symptoms, but it must be followed indefinitely or the benefit may eventually be lost. Table 1 describes an exercise regimen for treatment of PAD. If you do not have a treadmill, walk in your neighborhood or at a mall. Over time, you should notice an increase in the distance you can walk before you start to feel pain.

Exercise Type

Treadmill walking.

Intensity

Initial workload set at a speed and grade that causes pain at 3-5 minutes.

Exercise Pattern

Walk until moderate claudication pain is reached, then rest until symptoms subside. Repeat exercise-rest- exercise cycle.

Duration

Session lasting 35-50 minutes.

Frequency

Three sessions per week.

Supervision

Increase workload as walking ability improves so claudication pain always occurs with walking.

Program Length

At least 12 weeks.

Table 1. Exercise Regimen for Treatment of PAD

Baby aspirin – In general it is recommended that people over the age of 50 take a baby aspirin (81mg) every day to significantly decrease the risk of heart attack and stroke. However, aspirin can increase the risk of bleeding. Therefore, the risk-benefit ratio of taking aspirin should be determined for each person with PXE, and discussed on an individual basis with their doctor.

Medical therapies – Two drugs approved for the treatment of intermittent claudication are pentoxifylline (brand names Trental, Pentopak, Pentoxil) and cilostazol (brand name Pletal). *These drugs usually have minimal effect and are not without side effects.* Plavix is an anti-platelet medication used to prevent strokes and heart attacks. It cannot prevent narrowing of the blood vessels. It does keep platelets from forming a clot when blood vessels narrow and blood flow slows or when a plaque ruptures and blocks flow. In general it is given to patients who have stents in their arteries to help keep them open. Another medical therapy for intermittent claudication is statins, which are cholesterol-lowering medications to prevent progression of narrowing of the blood vessels and promote plaque stabilization.

Surgery – Surgery is reserved for when PAD becomes lifestyle limiting or when blood flow becomes critically low. An example of a lifestyle-limiting effect of PAD is being able to walk only one block before pain develops. Signs of critically low blood flow are a wound on the foot that will not heal or pain in the feet at rest. Surgical options include bypass, stenting, and angioplasty. However, the success of surgery or angioplasty depends on the type and location of the narrowing and the patency or quality of the vessels. Due to the effect that PXE has on the vessels, PXE can negatively affect the outcomes of surgical procedures done to improve blood flow. In general, maintaining vascular health and making adjustments in vascular risk factors are favored over surgical procedures for the treatment of PXE patients with vascular disease.

How to Reduce your Risk of PAD

One of the best things you can do to reduce your risk of PAD and all vascular diseases is practice a healthy lifestyle. Below are some practices you can adopt in order to prevent and

treat the signs and symptoms of vascular disease in PXE. Even though many of these measures may have no direct effect on PXE, peripheral vascular disease is often multifactorial and the risk factors and causes can be additive, so as many as possible need to be addressed.

1. Eliminate tobacco products

Smoking or any form of tobacco use is the *most important preventable risk factor* for vascular disease. Nicotine found in cigarette smoke injures the inside lining of blood vessels and can accelerate atherosclerosis progression by 10 to 50 times. Smoking doubles the risk of death and amputation with vascular disease. Disease severity is related to how many cigarettes you smoke a day and for how long you have been smoking. If you have PXE and you are a smoker, it is extremely important that you quit. There are various tools you can use to help you stop smoking, such as nicotine patches, nicotine gum, medications and smoking cessation programs. Your physician and counseling can help you succeed in quitting.

2. Eat a heart-healthy diet

A heart-healthy diet is a diet high in fruits, vegetables, whole grains, and fiber. It is also low in fat and cholesterol. It is important to include omega-3 fatty acids in your diet, which have been shown to decrease inflammation, lower blood pressure, and decrease the progression of vascular disease. Eat foods high in omega-3 fatty acids such as two servings of fish per week or take vitamin supplements.

Even though PXE causes calcification, this does not mean you should avoid calcium in your diet. Make sure you get the minimum daily requirement of calcium to maintain your bone health. Getting the recommended daily amount of magnesium may also be important.

3. Enjoy regular physical activity and maintain a healthy weight

There are numerous benefits to regular physical activity. Exercise has been shown to lower blood pressure, increase the good cholesterol in your blood, control blood sugar, reduce feelings of stress, control body weight, make you feel good about yourself, and slow progression of vascular disease. Maintaining a healthy weight can lower your risk of death from cardiovascular disease. It will also help you control your blood pressure and lipid levels.

4. Control your blood pressure

High blood pressure, also known as hypertension, is a significant risk factor for vascular disease. High blood pressure, known as the silent killer, causes an injury to the inner lining of the blood vessel wall. Calcification of the elastic layer of blood vessels in PXE can cause a lack of compliance (elasticity) in these vessels and can cause early onset hypertension. Thus, aggressive blood pressure control is very important. You can control your blood pressure with a combination of medication, diet, and lifestyle changes.

5. Control your cholesterol and lipid levels

High lipid levels and high cholesterol (hyperlipidemia) significantly increase your risk of vascular disease, particularly stroke and cardiovascular disease. Eating a heart-healthy diet and exercising are important to manage hyperlipidemia.

After diet, statins are the first-line lipid-lowering therapy. Statins are a class of drugs that lower cholesterol levels and stabilize plaques. Statin use can decrease your risk of heart attack and stroke. Side effects of statins include liver damage and leg cramps, which is also a symptom of vascular disease. Thus, if you develop leg cramps after you start taking a statin, it may be due to the statins and not vascular disease. If you have PAD, some doctors recommend taking a statin as a preventive measure even if your cholesterol/lipid levels are acceptable.

6. Control diabetes

Diabetes is a chronic disease marked by high levels of sugar in the blood. Diabetes increases the buildup of plaque and calcification in the blood vessels due to the chronic inflammatory state it creates. In fact, one in three people over the age of 50 with diabetes will also have PAD. If you have diabetes, it is important to keep it under control, especially if you have PXE. Even though control of diabetes has not been shown to decrease the risk of PAD, control of diabetes can help reduce the rate of cardiovascular events and decrease microvascular complications in the eyes and kidneys.

7. See your doctor regularly

It is important to see your doctor regularly, receive yearly vascular exams, and get your cholesterol levels checked. Other tests your doctor may want to perform include homocysteine and C-reactive protein levels. Homocysteine is an amino acid that your body needs and uses, but when elevated can increase your risk for vascular disease. C-reactive protein is a non-specific marker for systemic inflammatory disease.

Conclusion

Take control of your vascular health! Managing and modifying your risk factors as described can make a huge difference in your quality of life and help you live longer. In general, peripheral vascular disease can be followed by non-invasive testing and treated with conservative measures. Maintaining vascular health and healthy adjustments in vascular risk factors are favored over surgical procedures for the treatment of PXE patients with vascular disease.

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