Information for Clinicians

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Pseudoxanthoma elasticum (PXE) is an autosomal recessive, systemic, disorder, the hallmark of which is dystrophic mineralization of elastic tissue of the skin, retina, and arteries. PXE is caused by mutations in the gene which codes for the membrane transport protein ABCC6. Experiments on PXE knockout mouse pinpointed a circulating metabolite, pyrophosphate, that is implicated in this mineralization. PXE generally affects skin and eyes in everyone, and gastrointestinal and vascular systems in some. The primary care physician may be the first to suspect and diagnose PXE because of these varied clinical manifestations involving several body systems. They may also coordinate the lifelong specialty care of the affected patient and may be expected to be an authoritative resource as well as source of support for the patient and their family.

Incidence

PXE is a rare disease. Published reports estimate incidence at 1/25,000-100,000. The true incidence is unknown, as it is likely that affected individuals with mild involvement and/or atypical presentation escape diagnosis. It affects all races and ethnicities and is reported twice as frequently in women than in men. The reason for this gender discrepancy is not clear.

Skin manifestations

The *primary lesion* of PXE is a small 2-5 mm yellowish or flesh colored papule, irregular or rhomboid in shape (hence the misnomer of a term: *pseudoxanthoma*), which may form groups or coalesce into larger plaques. The lesions are *asymptomatic* and tend to be distributed symmetrically on flexural areas progressing downward from the neck to the axillae and antecubital fossa, and later to the groin and popliteal fossa. Less common areas of involvement include the periumbilical area, oral, and anogenital mucosa. Oral lesions, seen on the inner aspect of the lower lip, resemble Fordyce spots.

The lesions may give the affected skin a cobblestone appearance. The lesions may cause the skin of the neck to appear unwashed. Differential diagnosis includes the common entity solar elastosis as well as fibroelastolytic papulosis (PXE-like papillary dermal elastolysis), which can appear clinically identical to PXE.

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The skin lesions develop during childhood or adolescence, and progress slowly and predictably with age, progressing to other flexural areas. The neck, axillae, groin, or face may sometimes manifest lax, redundant folds of skin in late stage PXE.

Skin biopsy of lesional (and sometimes nonlesional) skin confirms the diagnosis if it shows calcification of fragmented, clumped elastic fibers in the mid and lower dermis. The highest yield is from biopsy of a primary lesion (papule). In the absence of primary lesions, punch biopsy of neck, axillary and/or antecubital fossa is recommended.

The skin lesions are asymptomatic. However, affected individuals with unsightly redundant folds can undergo surgical correction, in most cases with satisfactory wound healing. This should be described as reconstructive surgery for a congenital abnormality so that insurance will cover it. It is not cosmetic surgery.

Although skin manifestations are most characteristic of PXE, the ocular and cardiovascular manifestations are responsible for the morbidity of the disease. Indeed, in some cases, particularly in men, the skin lesions are barely visible.

Retinal Disease

The earliest, and often subtle, manifestation of PXE in the retina is peau d'orange, a diffuse yellowish mottling of the fundus usually seen in the first two decades of life. The characteristic retinal lesion is the angioid streak, seen in almost every affected adult, and often seen in childhood or adolescence. Angioid streaks are gray to brown or dark red, spoke-like bands radiating out from the optic disc or encircling the disc with peripapillary streaks. Angioid streaks correspond to breaks in Bruch's membrane, an elastin rich layer of the choroid. Neither angioid streaks nor peau d’orange affect visual acuity; however, subretinal neovascular capillary nets can grow through these breaks, leading to hemorrhage and central visual loss (not true blindness) if they occur in the macula or fovea.

Current treatments for age-related macular degeneration (AMD), the intraocular injection of the anti-angiogenic drugs, Bevacizumab (Avastin), Ranibizumab (Lucentis), and Aflibercept (Eylea) are now widely used in PXE and appear to be as effective as they are in AMD.

No longer first line treatments, laser photocoagulation and photodynamic therapy were used in PXE to seal bleeding or leaking blood vessels, with disappointing results. Laser treatment might stabilize vision and stop bleeding but causes scarring and loss of vision in the target area, and there is a high recurrence rate of new vessels. Photodynamic therapy results with PXE have also been disappointing, although a few patients have had good results. However, there is also a high rate of recurrent neovascularization.

Vascular Disease

The basic vascular pathology in PXE is dystrophic calcification of the abnormal elastic fibers in the internal elastic lamina and media of middle-sized arteries. These lead to changes resembling atherosclerosis leading to vascular stenosis or fragility. The most common manifestations of arterial disease in PXE are diminished peripheral pulses (including the upper extremities) and intermittent claudication. Angina and symptoms of intestinal ischemia may occur relatively early in life. Hypertension may be more common among affected individuals with PXE, though this is not known definitively. If present, this increases the risk of vascular complication in the individual affected by PXE and needs to be well controlled. Uncommonly, dramatic GI bleeding, usually gastric, may be an early manifestation and even the presenting sign of PXE. The mechanism is unknown, but gastroscopy shows gastric mucosal changes resembling mucosal PXE elsewhere (yellowish papules), and the histology of the gastric vessels resembles that of other arteries affected by PXE.

Genetics of PXE

PXE is an autosomal recessive disorder, despite old reports that both recessive and dominant PXE exist. For historical reasons, catalogues such as the Online Mendelian Disorders of Man (OMIM) continue to list a dominant form, there are no confirmed autosomal dominant cases. There are families in which two generations have PXE, and when tested, these have been shown to be pseudodominant due to an affected individual having a child with a carrier. The carrier frequency may be higher than previously thought and some recessive carriers may have mild subclinical manifestations on biopsy. Clinical expression is not helpful in predicting the severity in other family members as there is no evidence of correlation between genotype and phenotype. PXE has variable expressivity and environmental influences may modify the clinical expression. The gene is on the short arm of chromosome 16 (16p13.1) and encodes the ATP-binding cassette sub-family C member 6, *ABCC6*. Although the mechanism of action is not completely understood, there is evidence that disease-associated low levels of inorganic pyrophosphate in the blood cause mineralization in peripheral tissue.

Genetic testing is widely available. PXE International, the CEO of which materially participated in the gene discovery and she and others discovered and patented the gene and turned it over to PXE International. PXE International licensed the gene and its test to GeneDx, which still performs the test. The test can be useful for confirmation of an uncertain clinical diagnosis, identification of at-risk family members (siblings of the proband), and/or prenatal diagnosis. Please contact the PXE International office at 202.362.9599 for further details if you are unable to find testing.

Workup of the Affected Individual

General workup of the individual affected by PXE should include:
- A history detailing onset of signs or symptoms, detailed cardiovascular and ocular history, as well as family history.
- Examination of the skin, with special attention to neck and flexural creases as well as lip mucosa, including peripheral pulses.
- Confirmation of diagnosis by skin biopsy with appropriate special stains (von Kossa) for elastic tissue and calcium.
- Laboratory evaluation of lipids.
- Examination of siblings when feasible.

Ophthalmologic consultation should include:
- Dilated direct and indirect ophthalmoscopic exam.
- Fluorescein angiography and optical coherence tomography, if clinically indicated.
- Amsler grid monitoring of central visual fields by patient.

Cardiovascular consultation should include:
- Non-invasive studies of the peripheral vasculature (Doppler ankle-brachial ratios), if clinically indicated.
- Baseline stress test and sonogram of heart valves.
- EKG's (if symptoms or clinical findings warrant).

Management of Affected Individuals

As are most genetic diseases, PXE is incurable. Management should focus on education of the affected individual, monitoring and treatment of complications, and dietary and lifestyle modifications to delay or possibly prevent complications. This may involve a team approach including dermatologist, primary care physician, ophthalmologist, cardiologist, vascular surgeon, plastic surgeon, genetic counselor, nutritionist, and support groups. Support groups are of tremendous benefit in helping affected individuals cope with the disorder.

The affected individual (or parent) needs to be educated in understandable terms regarding the various manifestations of the disease and the prognosis (which is not as dire as some affected individuals are led to believe). Genetic testing is available and is most useful when a young person is diagnosed and his or her siblings may be too young to exhibit clinical manifestations. Not all mutations are found through genetic testing, so it is not 100% reliable. Genetic testing is costly, is not predictive of severity, and may not be conclusive. Regular ophthalmologic examination by a physician with expertise in retinal disease is essential and affected individuals should learn to use the Amsler grid to monitor for central visual disturbances. Avoidance of contact sports without appropriate protective goggles for sports is suggested to prevent eye trauma that could cause retinal hemorrhage. It is also possible that heavy contact sports like football with high impact could cause retinal bleeds as well. Regular physical examinations with specific attention to the cardiovascular system are essential. Lipid levels should be monitored periodically.

Surgical intervention may be indicated for gastrointestinal bleeding, severe peripheral vascular disease (if correctable), and the improvement of congenital abnormalities of the face, neck, axilla, and groin.

Weight control, avoidance of smoking, and aggressive management of hypertension and lipid disorders are all essential in delaying or reducing the severity of vascular complications. Pentoxifylline (Trental) and cilostazol (Pletal) may be of value in managing claudication, but this recommendation should come from a vascular specialist. Aspirin and other non-steroidal anti-inflammatory medications should be avoided due to the risk of gastrointestinal hemorrhage unless the benefits are felt to outweigh the risk and no safer alternative is available.

Most women with PXE have normal pregnancies. PXE in not associated with markedly increased fetal loss or an increased risk of adverse reproductive outcomes. Fetal complications due to impaired uteroplacental blood flow do not appear to be a problem. The incidence of gastric bleeding and retinal complications is lower than previously thought (<1%). There is no basis for women affected by PXE to avoid becoming pregnant.

A study of mammography in PXE showed that there is an increased incidence of microcalcifications, vascular calcification and skin thickening but no increase in breast cancer due to PXE. The pattern of breast microcalcification in PXE is benign and does not suggest cancer. The finding of skin thickening, skin calcification, breast microcalcifications, or vascular calcification in mammography should suggest a diagnosis of PXE.

Testicular microlithiasis has been observed in males with PXE, and a study suggests an association between PXE and testicular microlithiasis. In all males examined in one study, testicular microlithiasis was not associated with cancer.

Potential Treatments

It was reported long ago that high calcium intake early in life may correlate with the overall severity of PXE, but this was never confirmed by studies, and calcium restriction is unproven in the management of PXE. Calcium restriction can also lead to development of osteoporosis. It is recommended that calcium intake should be at the RDA and supplementation avoided unless dietary intake is known to be inadequate, or there is evidence of osteopenia or osteoporosis.

Reduced plasma levels of PPi, and consequently low PPi/Pi ratio, allows ectopic mineralization of soft connective tissues to ensue. Consequently, supplementation of diet with PPi intuitively makes sense. However, PPi has a very short half-life in plasma, and it is unclear in what quantities and how frequently it should be taken by the patients to effectively counteract the mineralization phenotypes. We have begun such studies. We have also tested magnesium, but further study is needed. Others have tested the efficacy of bisphosphonates, particularly etidronate, a stable structural and functional analogue of PPi, for its efficacy in preventing ectopic mineralization. Preclinical animal studies revealed that etidronate is effective in

preventing the mineralization in mouse models of PXE, and early clinical trials have shown its efficacy against vascular mineralization in patients with PXE.

PXE International, Inc. maintains a Blood and Tissue Bank and an international clinical registry. Affected individuals should be encouraged to register with PXE International to avail themselves of up-to-date information about PXE and to contribute to the advancement of knowledge about this rare disease. PXE International's medical advisors also serve as a resource for physicians caring for patients with PXE and can be contacted by email info@pxe.org, or phone, 202.362.9599.

Bibliography

For more information on pseudoxanthoma elasticum, please visit the PXE International website at http://www.pxe.org

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