Clinical and genetic aspects of pseudoxanthoma elasticum
Plomp, A.S.

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Proposal for updating the pseudoxanthoma elasticum classification system

Astrid S. Plomp, Johan Toonstra, Arthur A.B. Bergen, Marijke R. Canninga-van Dijk, Paulus T.V.M. de Jong

(2009, submitted)
ABSTRACT

Pseudoxanthoma elasticum (PXE) is a systemic disorder affecting elastic tissues most markedly in skin, retina and blood vessels. It is caused by mutations in the ABCC6 gene and is transmitted in an autosomal recessive way. In 1994 a new classification system for PXE was published as the result of a consensus conference. Since then the ABCC6 gene has been discovered, leading to new insights. We think that, at the present time, there is a need for a classification system incorporating all relevant systemic symptoms and signs, based on standardized clinical, histological and molecular biological examination techniques. We re-evaluated the histopathologic PXE signs and propose a classification system with unambiguous criteria leading to a consistent diagnosis of definite, probable or possible PXE world-wide.

Key words: pseudoxanthoma elasticum, PXE, classification, ABCC6
INTRODUCTION

Pseudoxanthoma elasticum (PXE) is an autosomal recessive disorder affecting elastic fibers mainly in skin, eyes and blood vessels. Although dermatological signs are common, the main burden of PXE is formed by the complications in the visual and cardiovascular systems [1]. The prevalence of PXE is estimated to be between 1:25,000 and 1:100,000 without an apparent geographic or racial predilection [2].

Although treatment options for cardiovascular and eye problems due to PXE are limited, transparent criteria and algorithms to make a diagnosis of PXE are necessary for several reasons. PXE patients have an increased risk of cardiovascular diseases, and extra attention to treatable risk factors for these diseases is warranted [2, 3]. Trauma to the head and/or eye should be especially avoided, because even slight trauma can cause retinal hemorrhage. NSAID's, especially aspirin, and anticoagulant drugs should be restricted in PXE patients, to prevent gastro-intestinal hemorrhages [2, 3]. A reliable diagnosis is also important should therapy for PXE become available in the future, for controlled clinical trials, for comparing research results and for genetic counseling. Siblings of a PXE patient have a risk of 25% to be affected as well and might wish to be informed and examined.

The most recent PXE classification we are aware of dates from 1994 and originated from a consensus conference [4]. We think that this classification system could be improved in several aspects, if only because at that time the PXE gene was unknown. In 2000 the PXE gene (ABCC6) was found [5-7] and to date over 200 mutations have been reported [8, 9].

The purpose of this paper is to propose a classification system for PXE that takes into account the systems and organs that are most frequently involved in PXE according to our present knowledge. We will start with an historical overview of previous classifications, the rationale for a new classification system, and an update on clinical signs and symptoms of PXE. Next we will propose updated criteria for the diagnosis of PXE and an algorithm that will classify a person as having definite, probable, possible or no PXE.

PREVIOUS CLASSIFICATION SYSTEMS

Based on an extensive literature study and his experience with 121 patients, Pope proposed in 1974 four different subtypes of PXE: autosomal dominant types I and II, and autosomal recessive types I and II. Patients were allocated to a certain subtype based on poorly defined clinical symptoms and signs and, if applicable, on the most probable mode of inheritance according to the pedigree [10-12]. Neldner (1988) studied 100 PXE patients with the criterion for inclusion being a biopsy-proven diagnosis of a characteristic skin lesion from a flexural site [13]. This selection criterion eliminated all potential PXE cases without characteristic skin lesions or typical histology. Neither Neldner nor others could classify all their patients according to the four subtypes, as proposed by Pope [4, 13, 14].

A consensus conference in 1992 resulted in publication in 1994 of diagnostic criteria for PXE
(Table 1) and a classification of patients into two major categories [4]. Category I patients were classified as certain PXE cases and had to have three major criteria: characteristic skin signs, characteristic ocular signs and characteristic histopathologic skin signs in PXE lesions. Category II patients were classified as uncertain PXE cases. Category IIa patients had angioid streaks (AS) and two minor criteria: elastic fiber calcification of nonlesional skin and PXE in a first-degree relative. Category IIb had AS and elastic fiber calcification of nonlesional skin only, IIc had AS and PXE in a first-degree relative, while category IId had no AS but two minor criteria, elastic fiber calcification of nonlesional skin and PXE in a first-degree relative. The authors noted that especially the classification of patients without characteristic skin signs was controversial, and that they could be heterozygous carriers of a recessive gene, have a mild form of autosomal dominant PXE or develop skin signs later in life.

In a recent diagnostic flowchart for PXE [8] patients were classified into the categories "definite", "probable" and "probably not" PXE after skin evaluation and funduscopy. In the last two categories additional skin biopsy or ABCC6 gene analysis were advised, but it was not mentioned how the results of these tests would influence the final conclusion. Family history was only considered to add in some cases to the degree of certainty of diagnosis. The aim of the flowchart was to define the role of skin biopsy and molecular analysis within the diagnostic work-up of a patient, not to make a new classification system [8].

**RATIONALE FOR A NEW CLASSIFICATION SYSTEM**

We think that the 1994 classification system can be improved in several ways.

1. It can be hard to decide whether criteria are met, especially for clinicians who do not frequently see PXE patients. PXE is a rather rare disease and the average time between the onset of PXE signs and the PXE diagnosis has been reported to be nine years [13].

2. In the 1994 paper the methods of examination were not defined. How many skin biopsies, from which sites and which histologic stains are minimally required? Is funduscopy for retinal signs sufficient or should fundus pictures be taken that can be compared or read by graders

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**Table 1. Criteria for the diagnosis of PXE in 1994 (Lebwohl et al.)**

<table>
<thead>
<tr>
<th><strong>Major criteria</strong></th>
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<tr>
<td>1. Characteristic skin involvement (yellow cobblestone lesions in flexural locations)</td>
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<tr>
<td>2. Characteristic histopathologic features of lesonal skin (elastic tissue and calcium or von Kossa stains)</td>
</tr>
<tr>
<td>3. Characteristic ocular disease (angioid streaks, peau d’orange, or maculopathy) in adults older than 20 years of age</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Minor criteria</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Characteristic histopathologic features of nonlesional skin (elastic tissue and calcium or von Kossa stains)</td>
</tr>
<tr>
<td>2. Family history of PXE in first-degree relatives</td>
</tr>
</tbody>
</table>
later on? Should retinal fluorescein angiography be performed to look for beginning AS, in case of non-specific peripapillary atrophy and no AS on fundoscopy?

3. According to the existing classification, a definite diagnosis of PXE can only be made when all three major criteria, “characteristic” skin signs, ocular signs and histopathologic skin signs are present (category I). With these three major criteria the diagnosis is indeed obvious and the use of criteria does not seem to add much. Recently the 1994 criteria were compared with molecular data [15]. Two $ABCC6$ mutations were found in 25 patients from 10 families, of whom 23 fulfilled the category I criteria. The authors did not find any PXE category I signs in 67 heterozygous carriers and 50 family members without any $ABCC6$ mutation [15]. These results seem to confirm the validity of category I of the 1994 criteria. In two patients with marked solar elastosis and severe macular degeneration the clinical and histological interpretation was not clear and they did not fulfill the category I criteria [15]. Also other PXE patients without macroscopic skin lesions have been reported [8, 16]. We have seen two patients, aged 56 and 57 years, who did not have any skin abnormality pointing to PXE, but had eye signs and two $ABCC6$ mutations. Therefore, we think that a definite PXE diagnosis can also be made in persons who do not meet all category I criteria. In addition, in the existing classification system it is not clear what it means when persons do not meet all three criteria and belong to category II. Is the diagnosis probable, possible or unlikely? No rationale for the different subcategories a to d of category II was given in the 1994 criteria, so that it was not clear what one should do with these. In the study of Christen-Zach et al. (2006) no homozygous patient, nor any heterozygous family member belonged to one of the categories IIa to d [15]. Some patients do not fit in any category of the 1994 classification system [17].

4. The classification would have to be revised when gene markers for PXE would be identified and characterized [4]. On the other hand, one should still be able to diagnose PXE also on clinical grounds. At present mutations can be detected in 66 to 97% of alleles [8, 9, 14, 18-21] and extensive molecular analysis of the gene is not yet routinely available. Having only one mutation or having two $ABCC6$ mutations without clinical signs is not enough to make the diagnosis, apart from the philosophical discussion when exactly a person is diseased. Before proposing a new PXE classification, we will address the points mentioned above and give an overview of the presently best known signs and symptoms of PXE. Where indicated, we will provide standard images.

**SIGNS OF PXE**

**Skin and mucosa**

*Clinical signs*

Typically, the skin shows yellowish xanthoma-like papules, with a diameter of 2-5 mm (Fig. 1a), which can coalesce into larger plaques (Fig. 1b). The first skin abnormalities are noted at a mean age of 13 years [13]. Their appearances were described as “cobblestone”, “Moroccan leather” and
“plucked chicken skin”. In 97% of 100 patients the lateral side of the neck was affected first, often followed by the axillae [13]. Less frequently other flexural sites of the body (antecubital and popliteal fossae, wrists, groins) are affected, as well as the periumbilical area. In some patients the lesions extend beyond the flexural sites in the course of time [3, 13]. The skin usually is affected in a symmetrical distribution [13]. In fig. 1a-d the variation in skin abnormalities can be seen. Lesions can also be present at the oral mucosa, especially at the inside of the lower lip, or
the anogenital mucosa [3, 13]. The skin can lose its elasticity, resulting in redundant skin folds (Fig. 1d,e) and prominent skin creases of forehead, chin and at the corners of the mouth (Fig. 1f) [1, 13, 22]. Three to four percent of PXE patients demonstrate hyperkeratotic papules with transepithelial elimination of altered elastic fibers resembling elastosis perforans serpiginosa [13, 23].

**Histopathological skin signs**

Light microscopy of affected skin, stained with Verhoeff-van Gieson elastic tissue stain, shows an increased amount of elastin. Elastic fibers in the mid dermis are short, fragmented, clumped and can become calcified (Fig. 2). Different calcium precipitates, among others CaCO$_3$ and CaPO$_4$, can be found. Calcium deposition in PXE can be best revealed by Von Kossa staining, which is specific for carbonate and phosphate radicals [13]. Above and below this abnormal zone in the mid dermis a zone with normal elastin and collagen is found. Scar tissue and clinically normal skin from flexural sites of PXE patients (and not of normal controls) can show
the same histologic abnormalities as clinically affected skin [16, 24]. An increased amount of proteoglycans has been found around and within affected elastic fibers. The meaning of this is not clear and it is not used for diagnostic purposes [1, 13, 22, 25]. Several authors found different abnormalities (increase, decrease, splitting, thickening, coiling, calcification) of collagen fibers in skin biopsies of PXE patients, visible with special stainings or electron microscopy, but others did not [13]. Flower-like deformation of collagen fibers in cross-section was found relatively frequent, but is aspecific [26, 27, 27-29]. Collagen abnormalities are considered not to be of primary significance [13].

In order to check the sensitivity and specificity of histopathology we took skin biopsies from 15 PXE patients from a genetically isolated population, homozygous for the c.3775delT mutation in ABCC6, from 41 relatives, heterozygous for the same mutation, and from 12 healthy control persons outside this population (Table 2). These were examined independently by two dermatopathologists with 5 and 25 years experience, who were masked for the origin of the biopsies. The combination of increased elastin, fragmented elastic fibers and calcium deposits is considered to be typical for PXE. This was indeed found in 19 of 20 biopsies from clinically affected skin of the PXE patients. In all these biopsies the elastin was typically clumped. Only one biopsy of affected skin showed increase and fragmentation of elastin, without clumping. In this biopsy calcification was also absent. Calcification was found in only one scar biopsy and not in the unaffected skin of the homozygous PXE cases, but the numbers of these biopsies were small. The combination of increased elastin, fragmented elastic fibers with clumping or calcium deposits was found in none of the heterozygous persons. Increase and fragmentation of elastin without calcification and clumping were found more often in the heterozygous group (63% and 57% respectively) than in the control group (29% and 48%). There were no morphologic differences between the fragmentation in these two groups. The important difference between the changes in elastin in homozygous versus heterozygous and control

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
 & cases & biopsies & increased elastin & fragmentation of elastic fibers & clumping & calcification \\
 & (n) & (n) & (%) & (%) & (%) & (n) \\
\hline
homologous cases* & 15 & 25 & 24 (96) & 22 (88) & 19 (76) & 20 (80) \\
\hline
-lesional skin & 20 & 20 (100) & 20 (100) & 19 (95) & 19 (95) \\
\hline
-non-lesional skin of a predilection site & 2 & 2 (100) & 1 (50) & 0 & 0 \\
\hline
-scar & 3 & 2 (67) & 1 (33) & 0 & 1 (33) \\
\hline
heterologous family members* & 41 & 68 & 43 (63) & 39 (57) & 0 & 0 \\
\hline
-predilection site & 36 & 25 (69) & 23 (64) & 0 & 0 \\
\hline
-scar & 32 & 18 (56) & 16 (50) & 0 & 0 \\
\hline
control persons & 12 & 21 & 6 (29) & 10 (48) & 0 & 0 \\
\hline
-predilection site & 12 & 4 (33) & 6 (50) & 0 & 0 \\
\hline
-scar & 9 & 2 (22) & 4 (44) & 0 & 0 \\
\hline
\end{tabular}
\caption{Histopathology of skin biopsies from homozygous PXE cases, heterozygous family members, and controls.}
\end{table}

*All coming from a genetically isolated population, having the same ABCC6 c.3775delT mutation
persons is that clumping and calcification were only present in homozygous persons. There was no intergrader nor intragrader variation in judging whether the histopathology was typical for PXE or not. There were only slight differences in scoring the extent of increase and fragmentation of elastin. Precise quantification of these features appeared to be difficult and not useful for diagnostic purposes.

We compared our findings with the literature. Bacchelli et al. (1999) examined eight skin biopsies from patients, 18 biopsies from asymptomatic putative heterozygous family members (based on haplotype analysis) and six biopsies from control persons [29]. By light microscopy they found increased elastin and elastic fiber polymorphism in all three groups, in patients more than in relatives, in relatives more than in controls. Elastic fiber mineralization was present in three relatives (markedly milder than in patients), as distinct from our results. Electron microscopy revealed mineralization in ten relatives. Martin et al. (2007) examined skin biopsies of two patients, seven heterozygous relatives and two relatives without a mutation [30]. They also found increase of elastin and abnormal elastic fiber morphology in the heterozygous relatives, midway between the two other groups. Mineralization was not reported.

We concluded that increase and fragmentation of elastin, in combination with the typical clumping and calcification, is characteristic for PXE, but their absence does not exclude PXE. The increase and fragmentation of elastin found in heterozygous persons can not be used as diagnostic criteria to identify carriers of PXE. Carriers might have mild elastic fiber calcification.

**Differential diagnosis of skin signs**

Skin abnormalities in several other conditions can resemble those in PXE clinically as well as histologically, especially in beta-thalassemia, sickle cell anemia, peri-umbilical perforating PXE, PXE-like phenotype with cutis laxa and multiple coagulation factor deficiency and after saltpeter contact [1, 3, 31]. Solar elastosis (Fig. 3a,b), fibroelastolytic papulosis of the neck, skin lesions in Buscheke-Ollendorff syndrome (osteopoikilosis with disseminated dermatofibrosis) and those after long-term penicillamine therapy can resemble PXE clinically, but do not show calcification of elastic fibers [1, 3, 32].

![Fig. 3a](image1.png)  Localized solar elastosis on the forehead of a 70 year old male.

![Fig. 3b](image2.png)  Redundant skin folds at the right side of the face and neck of an older female due to severe solar elastosis.
Eye

Clinical signs and symptoms

The first ocular sign often is peau d'orange of the retina (Fig. 4a). It is mostly located in the temporal part of the macular region. The peau d'orange sign may be quite variable in expression from a

Fig. 4. Eye abnormalities in PXE patients. a. Peau d’orange of the retina. b. Angioid streaks (arrows). c. Disciform macular degeneration. d. Punched-out lesions of the retina, some with a slightly depigmented tail (comets). e. Hyperpigmented paired wings (arrow) on each side of an angioid streak. f. Cuboid peripapillary atrophy.
hardly visible mottled aspect of the RPE up to markedly mottled pigmentation. Peau d'orange is one of the most typical ocular signs of PXE and remains asymptomatic for the patient. It was present in 96% of 100 patients, selected on skin abnormalities [13]. Peau d'orange has also been observed in patients with AS, who do not have skin signs of PXE [33]. Usually AS (Fig. 4b) are not seen before the age of 10 years. They are cracks in Bruch's membrane and do not produce symptoms, unless they approach the center of the macula. In the beginning, AS may be quite difficult to see and may be better visible on fluorescein and even more so on indocyanine green angiography than on ophthalmoscopy. Also AS can vary widely in extension and color. They may be reddish orange to dark red or brown [34], partly depending on the amount of choroidal pigmentation. The prevalence of AS was 99% in patients 20 years after their diagnosis of PXE [13]. With increasing age AS have the tendency to fade out and be replaced by patches of chorioretinal atrophy or scar tissue, sometimes with RPE hyperpigmentation [13, 35]. After 5-10 years most PXE patients having AS around the macular area will perceive metamorphopsia or distorted images. These are the result of fluid leakage from subretinal neovascular membranes arising from the choroid and growing through the breaks in Bruch's membrane, a so-called disciform reaction. Usually this is followed by hemorrhages from these membranes, eventually leading to disciform macular degeneration, scar tissue in the center of the macula (Fig. 4c), and severe central visual loss.

A very specific ocular sign in PXE is the "comet" lesion, which seems to be pathognomonic for PXE. This is a small, round, white punched-out lesion of the RPE and underlying choroid with or without a slightly depigmented tail (Fig. 4d). Comets are mainly located in the mid-periphery of the retina [1, 7, 34] and are asymptomatic. Also asymptomatic hyperpigmented paired smudges, like the "wings" of a hovering bird of prey, one on each side of an AS (Fig. 4e), seem to be typical for PXE and were reported in 50% of PXE patients [13]. Of the 15 homozygous cases from our genetically isolated population 60% had comets and 27% wings. Non-specific ocular signs of PXE are optic disk drusen and peripapillary atrophy. This atrophy often has cuboid instead of round borders, remnants of gradually disappearing AS (Fig. 4f).

**Differential diagnosis of eye signs**

Peau d'orange can resemble fundus abnormalities in an eye disorder much rarer than PXE. We observed it twice in autosomal dominant cystoid macular edema. AS have been reported as an isolated finding and in association with at least 41 other systemic conditions, of which the most important ones are beta-thalassemia, sickle cell anemia and Paget's disease of bone (osteitis deformans) [1]. PXE was detected in 24 to 86% of patients with AS [24, 33, 36, 37]. We are not aware of other disorders leading to comets or wings.

**The cardiovascular system**

**Clinical signs and symptoms**

It is well known that the risk of atherosclerosis is increased in PXE. Extensive cardiovascular examination was performed in 100 PXE patients, including measurement of blood pressure, ankle/arm index, exercise tolerance test, carotid artery pressures, electrocardiogram, serum lipid...
studies and history data on cardiovascular disease, tobacco use and alcohol use [13]. The most frequent findings were abnormal ankle/brachial ratio, abnormal treadmill run and intermittent claudication, all in about 30% of the patients. (Probable) angina pectoris was present in 13%, only one patient had experienced a myocardial infarction and one a cerebrovascular accident due to a ruptured cerebral aneurysm. The first cardiovascular symptoms were not usually noted until after age 30. Unfortunately these findings were not compared to a control group [13]. In another study 7% of 94 patients developed ischaemic stroke during a mean follow-up period of 17 years [38]. This was compared with data from the general population, which resulted in a relative risk of 3.6 for stroke in PXE patients under 65 years. Hypertension developed in 19%, angina pectoris in 16%, claudication in 16% and myocardial infarction in 2%, but these data were also not compared to a control group. Recently the prevalence of cardiovascular manifestations in 42 PXE patients was compared to the prevalence in the general population, also suggesting markedly increased risks for cerebrovascular incidents, peripheral artery disease, hypertension and intermittent claudication [8]. We are not aware of any study in which the incidence or prevalence of cardiovascular complications in PXE have been compared to an adequate control group. A few exceptional cases have been reported with cardiovascular symptoms in childhood [39-42]. Thickening of the endocardium and atrioventricular valves, mitral valve prolaps and restrictive cardiomyopathy have also been reported [1-3]. It has been suggested that persons with only one ABCC6 mutation have an increased risk for cardiovascular disease as well [43, 44], but these data have not yet been replicated by others. Gastrointestinal hemorrhage occurs in 8-19% of patients [1, 3, 13] and we are aware of one PXE case who had a gastric hemorrhage at age 15 years, 10 years before a diagnosis of PXE was made. In the general population the prevalence of gastrointestinal hemorrhage is about 1 per 1000 adults per year [45]. In conclusion, the exact risk for most of the cardiovascular signs and symptoms in PXE is unknown. Moreover, these signs and symptoms occur frequently in the general population and therefore seem at present too non-specific for PXE to include them in this diagnostic proposal.

Organ calcification

Multiple calcifications on ultrasound examination have been reported in breasts, kidneys, testicles, liver, spleen and pancreas of PXE patients [46-51]. These calcifications do not seem to cause any problems. They are not specific for PXE and at present we think that there are too few data on the exact specificity and sensitivity to include them as diagnostic criterion.

THE ABCC6 GENE

Inheritance of PXE is autosomal recessive [14, 52-54]. In 2000 the PXE gene, ABCC6, was cloned [5-7]. The relation between ABCC6 mutations and PXE pathology, clinical signs, and symptoms is still poorly understood. To date more than 200 different mutations have been found in PXE patients [8, 9]. Mutation analysis is complicated by the existence of at least two pseudogenes
of ABCC6, copies of part of the gene, which are not translated into protein [55-57]. The mutation detection rate in recent studies varied from 66 to 97% of alleles [8, 9, 14, 18-21].

REVISED DIAGNOSTIC CRITERIA

In order to obtain standardized and thus better comparable PXE criteria, we propose the following guidelines:
• Examination of the skin by a dermatologist or physician familiar with PXE.
• A skin biopsy from lesional skin or, if not applicable, from the lateral side of the neck and from a scar, stained with hematoxylin-eosin, Verhoeff-van Gieson stain for elastin and von Kossa stain for calcium deposits.
• Funduscopy (preferably including bio-microscopy with a slit lamp and 90 diopter lens) of the posterior pole of both eyes up to the equatorial region by an experienced ophthalmologist for peau d’orange, AS, macular degeneration, comets and wing signs. In a research setting, even more than in a clinical one, color photography of these fundus signs is recommended. Fluorescein or indocyanine green angiography is optional to look for beginning AS, if there is cuboid peripapillary atrophy but AS and other retinal PXE signs are not visible on funduscopy.
• We recommend exclusion of sickle cell anemia, beta-thalassemia and PXE-like phenotype with cutis laxa and multiple coagulation factor deficiency (caused by mutations in GGCX) by hemoglobin electrophoresis and examination of vitamin K dependent coagulation factors (II, VII, IX, X), if mutational analysis of ABCC6 is negative or not available (see comments).
The revised criteria and the proposal for a new classification system are given in Table 3.

COMMENTS

As distinct from previous classifications, we included in our revised criteria for PXE more specific ophthalmologic signs (comets and pigmented wings) as major criteria. Because the gene is now known, we also included results of mutational analysis of ABCC6 in the criteria. Based on our criteria, patients can be classified as having a definite, a probable, a possible or no diagnosis of PXE. Persons with all possible combinations of signs and symptoms can be placed into a category. A definite diagnosis can now be made in part of the patients, who did not fulfill the criteria for category I patients in the 1994 classification [4]. For example a patient with peau d’orange of the retina and a mutation in both alleles of the ABCC6 gene now has definite PXE as has a patient with PXE skin lesions at a flexural site of the body, a skin biopsy compatible with PXE, and comet-like lesions of the retina.

In our experience one of the main problems in diagnosing PXE in part of the patients is to decide whether there are skin abnormalities which point to PXE. The skin abnormalities are variable and especially solar elastosis can resemble the skin papules or plaques in PXE (Fig.3a)
and can also lead to redundant skin folds (Fig. 3b). Therefore, we added pictures of some variations in skin abnormalities in PXE (Fig. 1a-d) and of solar elastosis (Fig. 3).

In order to rule out as much as possible misclassification of signs, we propose several conditions that should be met when examining a patient. One of these is to exclude sickle cell disease, beta-thalassemia and PXE-like phenotype with cutis laxa and multiple coagulation factor deficiency, if mutational analysis of \textit{ABCC6} is negative or not available. These diseases rank highest in the differential diagnoses of AS. Based on the former criteria definite PXE could be diagnosed in some patients with sickle cell disease and beta-thalassemia. In both of these hemoglobinopathies PXE-like skin, ocular and vascular abnormalities can be found. Of 100 beta-thalassemia patients 16% had PXE-like skin signs (also on histopathology), 20%

### Table 3. Revised diagnostic criteria and integral classification system for PXE

<table>
<thead>
<tr>
<th>Major diagnostic criteria for PXE</th>
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<tr>
<td><strong>Skin category</strong></td>
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<tr>
<td>• Yellowish papules and/or plaques (Fig. 1a-d) on the lateral side of the neck and/or flexural areas of the body.</td>
</tr>
<tr>
<td>• Increase of morphologically altered elastin with fragmentation, clumping and calcification of elastic fibers in a skin biopsy (Fig. 2).</td>
</tr>
<tr>
<td><strong>Eye category</strong></td>
</tr>
<tr>
<td>• Peau d’orange of the retina (Fig. 4a).</td>
</tr>
<tr>
<td>• Minimal one angioid streak, each at least as long as one disk diameter (Fig. 4b). In doubt after confirmation on fluorescein or indocyanine green angiography.</td>
</tr>
<tr>
<td>• One or more ‘comets’ of the retina (Fig. 4d).</td>
</tr>
<tr>
<td>• One or more ‘wing signs’ in the retina (Fig. 4e).</td>
</tr>
<tr>
<td><strong>Genetic category</strong></td>
</tr>
<tr>
<td>• A mutation in both alleles of the \textit{ABCC6} gene.</td>
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<tr>
<th>Minor diagnostic criteria for PXE</th>
</tr>
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<tbody>
<tr>
<td><strong>Eye category</strong></td>
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<tr>
<td>• One AS shorter than one disk diameter.</td>
</tr>
<tr>
<td><strong>Genetic category</strong></td>
</tr>
<tr>
<td>• First degree family member (parent, sib or child) with a definite diagnosis of PXE.</td>
</tr>
<tr>
<td>• A mutation in one allele of the \textit{ABCC6} gene.</td>
</tr>
</tbody>
</table>

**Definite diagnosis PXE:**
the major genetic criterion and one major non-genetic criterion or three major criteria from the skin and eye category

**Probable diagnosis PXE:**
two major clinical criteria or one major criterion plus at least one minor criterion

**Possible diagnosis PXE:**
only one major criterion without minor criteria or only three minor criteria

Sickle cell anemia, beta-thalassemia and PXE-like phenotype with cutis laxa and multiple coagulation factor deficiency should be excluded, if mutational analysis of \textit{ABCC6} is negative or not available.
AS, and 10% had both skin signs and AS [58]. In a similar study of 40 patients over 30 years of age 55% had calcification of the posterior tibial artery, versus 15% of control patients [59]. In general these thalassemic patients are more mildly affected than PXE patients and they do not have mutations in $ABCC6$ [60]. These data suggest that the PXE features in these patients are secondary to the hematologic disease and not related to PXE. Also the differential diagnosis with PXE-like phenotype with cutis laxa and multiple coagulation factor deficiency can be difficult. The main differences are more severe and extended skin laxity, no vision loss and deficiency of the vitamin K-dependent coagulation factors in the latter. It is caused by mutations in the $GGCX$ gene [31].

We recommend that patients with a definite diagnosis of PXE be informed about prevention of the earlier mentioned complications and that genetic counseling be offered when appropriate. There is no consensus as to whether regular medical examinations are necessary, and if so, which ones exactly and with which frequency.

The question remains what to do with persons, who have a diagnosis of probable or possible PXE. The answer depends on the reason for asking this question. For (genetic) PXE research and comparison with normal control persons we tend to exclude probable and possible PXE cases. In a clinical context we think that those with a probable diagnosis of PXE should be regarded as PXE patients, if other relevant diseases have been excluded as far as reasonable. If a person with a probable or possible diagnosis is under age 30 more signs could develop later, so an examination could be repeated in five years time. Patients with a possible diagnosis of PXE could be heterozygous for an $ABCC6$ mutation. Mild PXE signs have been reported in putative heterozygous family members of PXE patients [29, 61]. Persons, who only have AS may be screened for Paget's disease, thalassemia and sickle cell anemia [33, 36].

When the functions of the $ABCC6$ gene become better known, diagnosing PXE might become easier. Evidence accumulates that PXE is a metabolic disorder with secondary abnormalities of elastic fibers [62, 63]. Knowledge about the involved metabolites could yield in the future new specific disease markers, which can be added to the criteria.

We fully appreciate that our proposed classification system is not perfect and like most classification systems will have to be updated in due time. More knowledge is needed about the sensitivity and specificity of the different clinical signs. A study of the phenotype in a large group of persons with two $ABCC6$ mutations and no other selection bias (as far as possible) would be necessary to validate this system and with the results from such a study the classification system could be further improved. Also contributions of other experts and new knowledge about PXE will lead to fine-tuning of this classification system in the future. For the time being, we hope that the proposed classification system may help clinicians to make the diagnosis of PXE and that it may improve comparison between studies and simplify pooling of future research data, thus speeding up the search for effective PXE treatments.
REFERENCES


Danielli L. Morphological changes in pseudoxanthoma elasticum and senile skin. Acta Derm Venereol Suppl (Stockh) 1979;1-79.


