Vascular Complications Developing in Family Members with Pseudoxanthoma Elasticum

Şeyda Figül Gökçe*, Burhanettin Çiğdem¹, Malik Ejder Yıldırım², Asli Bolayır³, Ayşe Vural Özeç⁴ and Sibel Berksoy Hayta⁵

¹Department of Neurology, Cumhuriyet University, Turkey
²Department of Genetics, Cumhuriyet University, Turkey
³Department of Ophthalmology, Cumhuriyet University, Turkey
⁴Department of Dermatology, Cumhuriyet University, Turkey

Abstract

Background: Pseudoxanthoma Elasticum (PXE) is a hereditary disorder characterized by the mineralization of the connective tissue. It generally begins with skin lesions. Ophthalmologic lesions develop later. Patients may present with complications ranging from peripheral vascular disease to cerebrovascular ischemic stroke and gastrointestinal bleeding with the addition of vascular involvement.

Methods: In this study it is revealed that the patient and her families with dermatological, ophthalmologic and genetically PXE diagnosed with ischemic stroke.

Results: Especially severe neurological damage of one of the siblings was noteworthy. Etiology was performed in patients with rare stroke or vascular complications with unexplained dermatological, ophthalmologic, vascular complications.

Conclusion: PXE must be kept in mind and the genetic counseling of these individuals constitute the essence of this paper.

Introduction

Pseudoxanthoma Elasticum (PXE) is a rare connective tissue disorder characterized by autosomal recessive inheritance with progressive mineral accumulation and fragmentation in the elastic tissues as a result of mutation in ABCC6 gene on chromosome 16p13.1 [1]. It affects the elastic structures of the skin, Bruch’s membrane of the retina and arterial vessel walls [2]. Patients present to clinics with skin, eye and vascular involvement. There has been a slight female dominance, and the clinical prevalence has been reported to vary between 1/25,000 and 1/100,000 [3]. Vascular complications of PXE include arterial hypertension, aneurysms and dissections, ischemic stroke, cardiac diseases, peripheral arterial diseases, and various hemorrhages [4]. The possibility of myocardial infarction due to early atherosclerosis and cerebrovascular diseases increases as a result of the mineralization and fragmentation of the middle-sized arteries and the aorta that develop in PXE; and this risk is further increased in the presence of lipoprotein composition and hypertriglyceridemia [5].

In this article, we present dermatological, ophthalmologic, radiological and vascular findings in a young female patient diagnosed with PXE, and referred to our clinic with an ischemic stroke and with a history of a third-degree parental consanguinity and her two siblings and mother. One of the siblings had a severe phenotype with recurring strokes, dementia and blindness starting at a young age, while the other had only faint skin findings. Faint dermatological findings like the ones on the brother of our index case can delay the diagnosis. The detailed family history and the recognition of faint dermatological findings especially on this wheelchair-dependent brother with dementia who was unable to see could have delayed the morbidity. The modifiable lifestyle recommendations for the index case and her sister could also have slowed down the progress of the disease early on. Moreover, the skin symptom of these patients in general is the first encountered symptoms. However, it is difficult for female patients to be diagnosed in this way in societies where the headscarf is widespread like ours, Turkish, society. For this reason, our female patients were diagnosed with ischemic stroke, as well. In the literature, it seems difficult to encounter cases that reflect findings that are as characteristic as the lesions in our index case and her sister. Finally, it is one of our intentions to emphasize the importance of genetic counseling in communities where
consanguineous marriages are common. We also wanted to remind lifestyle changes and, in this sense, appropriate medical treatments (recommendation of cholesterol lowering agents, avoidance of acetylsalicylic acid and nonsteroidal anti-inflammatory treatment) in these patients for whom treatment is not fully available [6,7].

Case Series

Case 1

A 54-year-old woman patient was admitted to our clinic with speech disorder, a shift towards right at the corner of the mouth, and weakness in the left hand. During the dermatological examination, loose skin in the neck (Figure 1A), umbilical region, bilateral antecubital and axillary regions (Figure 1B) as well as linearly-joined plaques (with an appearance of a pavement stone) and papular (ivory yellow papule) lesions were noticeable. Our patient’s mother and father were third degree relatives. Two out of four of her siblings also had similar skin lesions. In addition, one of these siblings (male) had recurrent strokes, blindness and dementia starting after age 35. Neurological examination revealed dysarthric speech, left central facial paralysis, and a slight paresis at the distal of the left upper extremity. Diffusion-weighted brain Magnetic Resonance Imaging (MRI) revealed areas of limited diffusion compatible with multiple, acute infarcts in the right periventricular white matter areas (Figure 2A,2B). No abnormality was detected in angiographic examinations. Angioid streaks and Peau d’orange appearance were observed in the retina during the patient’s eye examination (Figure 3A,3B). There was no symptom in the patient’s examinations for cerebrovascular disease etiology, with the exception of hyperlipidemia. In the skin biopsy of the patient, coarse, calcified, degenerative elastic fibers were observed in the middle and deep dermis. The findings were evaluated to be consistent with PXE. The relevant consultation and genetic analysis protocol was applied for genetic investigation. The patient was discharged with statin and lifestyle recommendations.

Case 2

The 58-year-old brother of the index case had a history of stroke attacks in the form of unilateral and bilateral paresis and imbalance, visual impairment, and progressive cognitive impairment, beginning at age 35. His history included an application of renal artery stenting. Dermatological examination revealed ivory yellow papular lesions and an appearance of cobblestone - although they were fainter than those of the index case - in the neck, nape and axillary region (Figure 4). Neurological examination showed cooperative impairment, pseudobulbar laughing and crying attacks, severe dysphasia, spastic tetraparesis (MRC 3/5), global vividness in deep tendon reflexes and extensor plantar responses. The patient had urinary and fecal
incontinence. Brain MRI showed widespread leukoaraiosis and periventricular lacunar infarcts (Figure 5). The ophthalmologic examination revealed that hemorrhages were noticeable, and also, there was an angioid streak and Peau d’orange appearance in the retina image of 2014 (Figure 6). In the examination of 2017, colloidal membranes were detected in the regions where hemorrhagic areas were previously observed, in addition to the angioid streaks and Peau d’orange appearance.

**Case 3**

There was no neurological deficit in the 38-year-old sister of the index case, but the dermatological findings were more prominent (Figure 7). There was no symptom in the patient history other than upper gastrointestinal bleeding. In the brain MRI, prevalent T2 and FLAIR hyperintense and T1 hypo intense signal changes were observed in periventricular and subcortical white matter areas (Figure 8) and Fundoscopic examination showed Peau d’orange appearance and angioid streaks (Figure 9).

**Case 4**

There was no symptom other than arterial hypertension in the history of the 71-year-old mother of the index case. No symptoms and lesions were detected in ophthalmologic, dermatological and neurological examinations. In the brain MRI, prevalent FLAIR hyperintense signal changes were observed in periventricular and subcortical white matter areas (Figure 10). The father of index case was not alive. Two brothers of the index case, who did not have any skin lesion or neurological and ophthalmologic complaints, could not be evaluated because they lived abroad.

**Genetic Analysis**

The disease is caused by the mutations of ABCC6 gene. Therefore, the full gene analysis of ABCC6 gene was performed by Next Generation Sequencing method. Loss-of-function mutation [c.3421>T (R1141X)] was found in exon 24 of the gene. This mutation was homozygous in the index case and her two siblings and heterozygous in her mother. Genetic and laboratory analyzes and data from patients are shown in Table 1. The revised diagnostic criteria for PXE are given in Table 2.

**Discussion**

PXE is a rare connective tissue disorder characterized by autosomal recessive inheritance with progressive mineral accumulation and fragmentation in the elastic tissues as a result of mutation in ABCC6 gene on chromosome 16 (16p13.1) [1]. In PXE, skin lesions occur in late childhood and adolescence, mostly in the form of yellow papules on the neck, nape, and antecubital, axillary and flexural areas. These lesions tend to coalesce reticulately over time, and the skin gets a loose, wrinkled appearance [8]. Less commonly, they also occur in the umbilicus, oral mucosa and anogenital region. Findings may increase in pregnancy [9]. The classical histopathological finding is the imaging of fragmented calcific fibrils in middle and lower dermis with specific stains such as Von Cossa [10]. In the later stages of the disease, irregularity of the retinal pigment epithelium leads to Peau d’orange appearance, while both calcification and thickening of the Bruch’s membrane and loss of pigment granules in the retinal membrane epithelium lead to angioid streaks. Calcification of Bruch’s membrane leads to fragility, followed by hemorrhage, resulting in visual loss with neovascularization [2]. Cerebrovascular stroke is the most commonly reported neurovascular symptoms in PXE. The balance.
between procalcific and anticalcific substances that shape the medial calcification as a result of mutation in ABCG6 gene changes in favor of calcification. In this respect, the plasma level of pyrophosphate, which is a strong inhibitor, decreases, and mineralization occurs in the media and intima layers of middle and small arteries [4,11]. Internal elastic fragmentation and calcification lead to the thickening of the intima layer of the vessel and the deterioration of the arterial structure similar to atherosclerosis. Cardiovascular causes such as hypertension in this condition also contribute to this pathology [12]. Aortic stenosis has also been reported in addition to the stenosis of medium-sized vessels such as radial and carotid artery stenosis [13,14]. Cardiovascular manifestations include decreased peripheral pulses, angina pectoris, hypertension, mitral valve prolapse or stenosis, restrictive cardiomyopathy, and sudden cardiac insufficiency resulting death. One of the most common cardiovascular symptoms is intermittent claudication [15-18]. Gastrointestinal hemorrhage may develop due to calcification of elastic fibers in small arteries under the mucosa [19]. PXE does not directly affect the central nervous system, but cerebrovascular disease may develop due to secondary reasons such as interruption of the blood stream based on arterial wall thickening or hypertension [20]. The most commonly reported neurological manifestation in PXE is ischemic stroke and is more frequent than in the normal population (relative risk 3.6) [10]. PXE is angiographically characterized by internal carotid artery and vertebral artery tortuosity, stenosis and occlusion, and is similar to angiographic findings of severe atherosclerosis. Large diameter collaterals resulting from carotid occlusion are similar to Moyamoya disease [21,22]. Fibromuscular dysplasia-like appearance has also been reported [23]. In addition to ischemic stroke, aneurysm formation, subarachnoid and intracerebral hemorrhage, and progressive cognitive decline may also develop in PXE [24]. As reported in our third case, gastrointestinal hemorrhage, especially gastric origin, can develop in PXE. In 10% to 15% of cases, there is a history of gastrointestinal bleeding [25]. Hereditary systemic diseases should be considered in the presence of dermatological and ophthalmologic symptoms, signs and family history in young stroke patients. In our index case, the absence of a risk factor for stroke other than hyperlipidemia and the presence of systemic findings and family history led to the suspicion of hereditary causes for stroke. The presence of yellowish papules on the neck and flexural surfaces brought to mind the diagnosis of PXE, and the findings of the skin biopsy confirmed the diagnosis. Peau d’orange and angioid streak findings detected in the ophthalmologic examination are also typical of PXE. In spite of the presence of two major diagnostic criteria, molecular genetic analysis also confirmed the diagnosis of PXE. The phenotype-genotype correlation was not perfect. In the case of the brother, the dermatological findings were backgrounded, and the neurological symptoms were dominant, which resulted in a delayed diagnosis. On the other hand, there was no neurological deficit in the sister whose dermatological findings were dominant. It should be kept in mind that all symptoms of the disease may not be of similar severity in all individuals. In the management of this disease, which cannot yet be fully cured, it is thought that the disease course can be modified by measures such as lifestyle modification, regulation of medications used, healthy diet, and frequent ophthalmologic examination [10]. Moreover, due to the autosomal recessive inheritance pattern, it is very important to make a correct diagnosis in order to be able to provide prenatal genetic counseling service. It seems important to try to remove the cardiovascular risk factors in this disease which is not yet fully treatable. As a lifestyle change, it may be advisable not to smoke, lose weight, walk, and exercise. Atorvastatin is an agent that can be used to regulate the lipid profile [26]. Due to the risk of ocular hemorrhage, acetylsalicylic acid is generally contraindicated in PXE. Similarly, nonsteroidal anti-inflammatory agents and antiplatelet agents should not be used because of the possibility of gastrointestinal bleeding [27]. However, this risk should be counterbalanced against potential benefits in prevention of thrombophilia. In the case of arterial stenosis, standard surgical bypass or percutaneous angioplasty can be performed to improve blood flow. However, in patients with calcified coronary arteries, surgical bypass is not recommended due to the increased risk of complications.

### Table 1: Patient Data.

<table>
<thead>
<tr>
<th>Age</th>
<th>Length (cm)</th>
<th>Weight (kg)</th>
<th>Laboratory</th>
<th>Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>First case</td>
<td>54</td>
<td>155</td>
<td>80</td>
<td>Hyperlipidemia, ABCG6 gene homozygous mutation</td>
</tr>
<tr>
<td>Second case</td>
<td>58</td>
<td>171</td>
<td>82</td>
<td>Hyperlipidemia, Microhematuria, ABCG6 gene homozygous mutation</td>
</tr>
<tr>
<td>Third case</td>
<td>38</td>
<td>158</td>
<td>71</td>
<td>Iron deficiency anemia, ABCG6 gene homozygous mutation</td>
</tr>
<tr>
<td>Fourth case</td>
<td>71</td>
<td>154</td>
<td>75</td>
<td>Hyperlipidemia, Iron deficiency anemia, ABCG6 gene heterozygous mutation</td>
</tr>
</tbody>
</table>

### Table 2: Revised diagnostic criteria for PXE (adapted from Lebwohl).

#### Major Diagnostic Criteria

| Skin | a. Yellowish papules and/or plaques on the lateral side of the neck and/or flexural areas of the body; or b. Increase of morphologically altered elastin with fragmentation, clumping and calcification of elastic fibers in a skin biopsy taken from clinically affected skin |
| Eye | a. Peau d’orange of the retina; or b. One or more angioid streaks (ASs), each at least as long as one disk diameter. When in doubt, fluorescein or indocyanine green angiography of the fundus is needed for confirmation. |
| Genetics | a. A pathogenic mutation of both alleles of the ABCG6 gene; or b. A first-degree relative (parent, sibling, child) who meets independently the diagnostic criteria |

#### For Definitive PXE, Minor Diagnostic Criteria

| Eye | a. One AS shorter than one disk diameter; or b. One or more ‘comets’ in the retina; or c. One or more ‘wing signs’ in the retina |
| Genetics | a. A pathogenic mutation of one allele of the ABCG6 gene |

#### Requirements for the Diagnosis of PXE

| Definitive Diagnosis | The presence of two (or more) major criteria not belonging to the same (skin, eye, genetic) category |
| Probable Diagnosis | The presence of two major eye or two major skin criteria, or, The presence of one major criterion and one or more minor criteria not belonging to the same category as the major criterion |
| Possible Diagnosis | The presence of a single major criterion, or, The presence of one or more minor criteria |

---

Seyda Figül Gökçe, et al., Neurological Case Reports

Revise diagnostic criteria for PXE (adapted from Lebwohl).
be performed [27,28]. The weakness of the vascular wall (especially in the distal veins) can change the choice of vessels in this patient group for surgical grafts. Considering the PE pathophysiology, reducing calcium intake as well as using investigational agents such as magnesium, bisphosphonate, and editronate seem to be able to create new approaches to reduce mineralization [29,30]. Frequent ophthalmologic examination is very important for the quality of life of the patients. Moreover, due to the autosomal recessive inheritance pattern, it is very important to make a correct diagnosis in order to be able to provide prenatal genetic counseling services.

**Conclusion**

PXE is a hereditary connective tissue disease, which may lead to ischemic stroke and may also be accompanied by dermatological and ophthalmological symptoms. In patients with an inexplicable cerebrovascular disease, PXE should be considered in the presence of systemic signs and symptoms, and family history.

**References**