Research letter

The extent of pseudoxanthoma elasticum skin changes is related to cardiovascular complications and visual loss: a cross-sectional study

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Dear Editor, Pseudoxanthoma elasticum (PXE) is a multisystem genetic disorder with cutaneous, ophthalmological and cardiovascular (CV) involvement.[1–3] Being able to predict the natural progression of PXE in various systems would improve preventive care in those patients at elevated risk of CV or ophthalmological complications yet, the required means are still lacking. It is unknown if each body system evolves at its own pace; however, the skin is typically involved earlier than other systems.[4] PXE skin lesions appear mainly in the first two decades of life; initially usually at the neck and progressively extending to other skin areas. This continues until around age 30 years.[5] CV and ophthalmological complications may develop later. We aimed to investigate potential associations between the extent of PXE skin changes and the severity of visual and CV manifestations.

We performed a retrospective analysis of clinical data in patients with confirmed PXE, and monitored at our referral centre from 2008 to 2015. PXE diagnosis was confirmed on the basis of distinctive skin lesions, dermal elastorrhexis, ophthalmological signs (peau d'orange, angioid streaks, retinal atrophy[2]) and/or two mutations of the *ABCC6* gene. The extent of skin involvement was estimated by enumerating the affected skin sites, and considering the 10 typical areas usually affected in most patients with PXE (lateral neck, anterior neck, nape, axillary fossae, shoulder joint region, antecubital fossae, groin, popliteal fossae, periumbilical region, mucosa of inner aspect of the lower lip), and nine nontypical areas (oblique mental creases, face, upper limbs excluding folds, lower limbs excluding folds, lumbar, genital, anal, oral mucosa excluding lower lip, other areas). 'Affected' areas had at least one lesion and we encoded for skin lesion presence (1) or absence (0), irrespective of severity. Severe ophthalmological involvement was defined as unilateral or bilateral blindness specifically associated with PXE (neovascular complications or primary atrophy[6]). Severe CV involvement was defined as medical history of heart attack and/or stroke and/or recourse to lower limb revascularization.

Data were expressed as median (interquartile range, IQR). Statistical analysis was performed using SPSS 15·0 for Windows. Mann–Whitney nonparametric testing for independent variables was done to compare patient groups with and without complications. Additionally, a multivariable logistic regression model was used to ascertain the effects of number of affected skin lesions, age and sex on the likelihood that patients have PXE complications. Relationships between number of affected skin areas and age were examined using Pearson's correlation coefficient (r). $P \leq 0{\cdot}05$ (two-tailed) indicated significance.

We included 125 patients (85 female; aged 10–79 years): 13% had severe CV involvement, 33% had blindness in at least one eye, and 21% had bilateral blindness. The number of affected skin areas was significantly higher in patients with severe CV involvement, bilateral blindness, and blindness in at least one eye (Table 1). A statistically significant association was found between number of affected skin areas, age, sex and development of complications (further detailed information can be obtained from the corresponding author).

As expected, patients with a medical history of severe CV involvement and/or blindness were significantly older (Table 1). However, the number of affected skin sites correlated only very slightly with age in all 125 patients (Pearson $r = 0{\cdot}3$, $P = 0{\cdot}00007$). For those over 30 years [n = 95; 51 (IQR: 18) years; 9 (5) affected sites], the number of affected

Table 1 Distribution of PXE complications according to number of affected skin areas and age

	n	Frequency, %	Number of affected skin areas, median (IQR)		Age (years), median (IQR)	
All patients	125 (85 F)	100	8 (6)		46 (28)	
Complication type[a]			With	Without	With	Without
Severe CV involvement	16 (9 F)	13	10 (4); $P = 0{\cdot}001$	8 (6)	58 (17); $P = 0{\cdot}006$	42 (28)
At least unilateral blindness	41 (24 F)	33	10 (3); $P = 5 \times 10^{-5}$	7 (7)	58 (12); $P = 8 \times 10^{-11}$	36 (23)
Bilateral blindness	26 (14 F)	21	11 (2); $P = 9 \times 10^{-5}$	8 (6)	59·5 (11); $P = 6 \times 10^{-8}$	40 (24)

F, female; IQR, interquartile range; PXE, pseudoxanthoma elasticum. [a]With complications vs. without complications (Mann–Whitney test).

skin sites did not correlate with age (Pearson r = –0·006, P = 0·9).

Our findings indicate an association between number of affected skin sites and severe CV events and/or ophthalmological complications of PXE, to date, not yet demonstrated in a large cohort. One study based on a much smaller cohort (14 Japanese patients with PXE, aged 52–85 years, four of 14 patients with PXE-associated CV events) reports similar results.[7] The authors rated six skin sites to obtain a total distribution score, and demonstrated that higher distribution scores were related to CV involvement and to the width of angioid streaks. Furthermore, the occurrence of mucosal lesions was associated with CV events.

One obvious limitation of our work is that our cross-sectional study was conducted at a single time point. However, there is virtually no prospect of obtaining data for longitudinal analysis in such a rare, slowly progressive condition as PXE. We speculate that extensive dermatological lesions might reflect a general predisposition to mineralization, which would further promote calcification in ocular and arterial tissue.

In conclusion, dermatologists should envisage closer monitoring of patients with PXE with extensive early skin signs, including careful supervision of CV risk factors (e.g. lifestyle adjustments such as stopping smoking and adopting regular moderate endurance exercise) and thorough prevention of head trauma to preclude eye involvement.

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