Intracranial aneurysms and connective tissue disorders
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Prevalence of symptomatic intracranial aneurysms and ischaemic strokes in pseudoxanthoma elasticum.

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Submitted for publication
Introduction

In pseudoxanthoma elasticum (PXE), a heritable connective tissue disorder, the elastic fibres of the skin, eyes, and cardiovascular system become slowly calcified leading to symptoms in these organs.\(^1\) The prevalence is estimated to be approximately 1 per 100,000.\(^1\) The mode of transmission can be both autosomal recessive and autosomal dominant \(^1\), indicating that it is a heterogeneous entity. The cause is unknown, although the locus for PXE has been mapped to chromosome 16p13.1.\(^2\)

PXE has been associated with intracranial aneurysms in several textbooks and reviews.\(^3\)-\(^6\) Such a relationship may be of great pathogenetic and clinical significance. This association might elucidate the pathogenesis of intracranial aneurysms, and screening of patients with PXE might be warranted in order to detect asymptomatic intracranial aneurysm. In addition, PXE may cause cerebral ischaemia by premature arterial occlusive disease.\(^7\)

After reviewing the literature on the possible relationship between PXE and symptomatic intracranial aneurysms or ischaemic stroke we performed this study to seek evidence for an increased prevalence of both in patients with PXE.

Patients and Methods

The records of all patients diagnosed with PXE at two major institutes caring for a large group of patients with PXE, the Netherlands Ophthalmic Institute in Amsterdam, and the departments of Dermatology and Ophthalmology at the University Hospital Nijmegen, were retrieved. Furthermore, during the annual meeting of the Dutch PXE Patient Society subjects not attending the Departments in Amsterdam or Nijmegen were invited to participate in the study. PXE was diagnosed on clinical symptoms following the Berlin Nosology \(^8\), and in some verified by a skin biopsy. All patients had been examined by an experienced ophthalmologist and dermatologist. We collected data on patient age, gender, and clinical manifestations. During the follow-up period, all patients were contacted by telephone, we investigated new manifestations of the disease, and inquired about newly developed symptoms and signs attributable to intracranial aneurysms, subarachnoid haemorrhages, or ischaemic stroke. Further details of medical events were retrieved by contacting the responsible physician.
For the literature review, we performed a Medline Search using the following key words in various combinations: PXE, Grönblad-Strandberg syndrome, (ischaemic) stroke, cerebral infarction, (a)symptomatic intracranial aneurysm, connective tissue disorder, and subarachnoid haemorrhage. We also followed all references from papers thus found, and traced references on this topic from several text books.\(^3\)\(^-\)\(^6\)

This study was approved by the institutional review boards of the participating centres, and the Medical Ethical Committee of the Academic Medical Centre of the University of Amsterdam. The 95% confidence limits of the number of events during follow-up was calculated using the Poisson method.

Results

The patient group comprised 100 patients, 37 male and 63 female. The mean age at first presentation was 31.7 years, ranging from 2 to 61 years of age. The presenting manifestations of all patients are listed in table 1. None of the patient with PXE had a history of subarachnoid haemorrhage or had presented symptoms or signs relating to an intracranial aneurysm when diagnosed with PXE. One patient presented with an ischaemic stroke at the age of 55 years. Skin biopsies, all diagnostic of PXE, were performed in 46 patients (46%). A family history positive for PXE was present in 47 patients (47%).

Table 1. Major presenting manifestations in 100 consecutive patients with pseudoxanthoma elasticum.

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired vision</td>
<td>69 (69%)</td>
</tr>
<tr>
<td>Typical skin lesion*</td>
<td>93 (93%)</td>
</tr>
<tr>
<td>Claudication</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Gastro-intestinal haemorrhage</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

*Lax, redundant, and relatively inelastic skin in flexures, exaggeration of nasolabial folds and chin.
In 94 patients (94%), with a mean age of 31.4 years, we obtained a follow-up. The mean follow-up was 17.1 years (range 1 to 49 years). This resulted in a total number of 1602 observation years. Complications that developed during the follow-up period are listed in table 2. One patient developed a gastric haemorrhage when using aspirin. In one patient hypertension resulted in renal failure. Four of the 15 patients with intermittent claudication had surgery for a femoral artery bypass graft, and coronary artery bypass grafting was performed in five of 15 patients with angina pectoris. In 14 patients a computerized tomography (CT) scan of the brain was made, showing cerebral infarction in eight patients, and no abnormalities in six patients (in these last patients the CT was made because of headache). Additional magnetic resonance imaging (MRI) of the brain was performed in three patients showing cerebral infarction. Two patients, with ischaemic strokes, had a cerebral angiography which revealed no aneurysms or other vascular abnormalities. Altogether seven patients developed an ischaemic stroke (rate 77/100,000/year, 95% confidence limits 238-861/100,000/year). For patient characteristics see table 3. None of the patients had symptoms or clinical evidence of large cerebral vessel disease. The cerebrovascular pathology was confined to the small vessels. Additional investigations revealed, besides a mild hyperhomocysteinaemia in one patient (patient 2), no other haematological abnormalities or vasculopathies as a cause for the ischaemic stroke. One patient had ipsilateral transient ischemic attacks before an ischemic stroke developed, and another patient had the ischemic stroke when already using aspirin. In general population the rate of ischemic strokes is 22/100,000/year. The relative risk in PXE was 21.7 (95% confidence limits 10.8/39.1). Five patients died; four (aged 50, 53, 59 and 61 years, respectively) of a myocardial infarction, and one of a major gastric haemorrhage (48 years of age). In 6 patients we were unable to collect follow-up data. Three had moved to an unknown location, and three did not want to participate in the study.

Our review of the pertinent literature revealed four patients with PXE and intracranial aneurysm. The characteristics of these patients are summarized in table 4.

The frequency of ischemic stroke in PXE is difficult to determine, since many reports of the patients are sketchy, do not specify, and were published a long time ago and so lack sufficient neuroimaging. The youngest patient described was an 11 year old girl, most patients were 45 years or older.
a series of 106 patients with PXE five had suffered a stroke. A study investigating the death of 12 patients with PXE revealed ischemic stroke as cause in four, and cerebral haemorrhage as cause in two patients. The cerebral haemorrhage was not further specified.

Table 2. Complications that developed during a mean follow-up period of 17.1 years in 94 patients with pseudoxanthoma elasticum.

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further impairment of vision</td>
<td>52 (55%)</td>
</tr>
<tr>
<td>Exacerbation of skin symptoms</td>
<td>22 (23%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (19%)</td>
</tr>
<tr>
<td>Gastro-intestinal haemorrhage</td>
<td>17 (18%)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>15 (16%)</td>
</tr>
<tr>
<td>Claudication</td>
<td>15 (16%)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Severe skin haemorrhage</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Severe nose bleeding</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Severe uterine haemorrhage</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Death</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Pyrosis</td>
<td>4 (4%)</td>
</tr>
</tbody>
</table>

Table 3. Characteristics of ischaemic strokes in 7 patients with PXE.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age*</th>
<th>Sex</th>
<th>Hemiparesis</th>
<th>Hypertension</th>
<th>Cigarette smoking</th>
<th>Cardiac diseases</th>
<th>Peripheral vascular disease</th>
<th>Brain imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>M</td>
<td>Left</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>CT: no abnormalities</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>F</td>
<td>Right</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>MRI: MIVL bilateral</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>F</td>
<td>Right</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>CT: MIVL bilateral</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>M</td>
<td>Left</td>
<td>no</td>
<td>no</td>
<td>yes; ischaemia</td>
<td>yes</td>
<td>MRI: MIVL bilateral</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>F</td>
<td>Left</td>
<td>no</td>
<td>no</td>
<td>yes; ischaemia</td>
<td>yes</td>
<td>MRI: MIVL bilateral</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>M</td>
<td>Right</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>CT: MIVL bilateral</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>F</td>
<td>Left</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>MRI: no abnormalities</td>
</tr>
</tbody>
</table>

*Age at which stroke occurred; CT = computerized tomography; MRI = magnetic resonance imaging; MIVL = Multiple ischaemic vascular lesions.
Table 4. Characteristics of the patients with PXE and an intracranial aneurysm as described in literature.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Sex</th>
<th>Age*</th>
<th>Angioid streaks</th>
<th>Typical skin lesions</th>
<th>Localization aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Female</td>
<td>29</td>
<td>yes</td>
<td>not mentioned</td>
<td>subclinoid aneurysm right ICA</td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>66</td>
<td>yes</td>
<td>not mentioned</td>
<td>right ICA parasellar</td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>20</td>
<td>yes</td>
<td>yes</td>
<td>right cavernous sinus (arteriovenous fistula)</td>
</tr>
<tr>
<td>13</td>
<td>Female</td>
<td>66</td>
<td>not mentioned</td>
<td>yes</td>
<td>aneurysm cavernous portion right ICA</td>
</tr>
</tbody>
</table>

Ref = reference number; *Age of patient when intracranial aneurysm became symptomatic; ICA = internal carotid artery.

Discussion

In our population of patients with PXE no symptomatic intracranial aneurysm occurred or became clinically overt during follow-up.

The relationship between PXE and intracranial aneurysm, as suggested in the literature, is based on a small number of case reports of intracranial aneurysms in patients with PXE. In these cases no pathological data or other evidence was presented pointing to a causal relation. In addition to these four patients with PXE and an intracranial aneurysm, Sharma described a patient with PXE and subarachnoid haemorrhage in whom cerebral angiography showed no intracranial aneurysm. Goto described a patient with PXE and a fusiform aneurysmal dilatation of the basilar artery and left ophthalmic artery, with complete occlusion of the left internal carotid artery. It is conceivable that this obstruction of the left internal carotid artery may have increased the strain in the vertebrobasilar system. Other craniocervical vascular malformations described in patients with PXE are fusiform cervical aneurysm, pontine arteriovenous malformation, bilateral calcified common carotid aneurysms, carotid rete mirabile, and an aneurysm of the anterior spinal artery. The last patient had stenosis of the abdominal aorta, and dilatation of internal thoracic arteries. As the anterior spinal artery is an important collateral pathway, this aneurysm may have developed secondarily to haemodynamic stress.

Brain autopsy reports of two patients with PXE have not shown macroscopic intracranial aneurysms or pouch formation of cerebral vessels, and cerebral angiograms in three patients with PXE showed no intracranial aneurysm. Also, one large clinical and descriptive series of 106 patients,
and a review of 204 patients with PXE do not mention symptomatic intracranial aneurysms.\textsuperscript{19,29}

The absence of intracranial aneurysms in our patient series does not exclude future development of intracranial aneurysms. Our PXE patients had an average age of 31.9 years at presentation. We found no evidence of intracranial aneurysms over a total retrospective (3168 years) and prospective (1602 years) follow-up period of 4770 years. The 95% confidence limits of these findings are 0 to 0.0008 events per year. In population studies the incidence is about 0.001 subarachnoid haemorrhages per year.\textsuperscript{30} This does not refute any correlation between the two entities, but is certainly not suggestive of a strong relation. The case histories in the literature probably represent mere fortuitous coincidence.

Ischaemic stroke was present in one patient as a presenting manifestation, recurred in the same patient, and developed during follow-up in six other patients. PXE patients have a clear excess of ischaemic strokes, we estimated a relative risk of 21.7. Focal cerebral ischaemia in PXE is predominantly caused by small-vessel occlusive disease, with hypertension, also common in PXE, as an accelerating factor as was suggested before.\textsuperscript{7,18,27} Our findings strongly confirm this relationship. Preventive treatment in patients with PXE and an ischaemic stroke is controversial. After acute ischemic stroke, antiplatelet treatment (aspirin) is advised for secondary prevention, and it should be administered within 48 hours of the stroke onset.\textsuperscript{31} However, our data show that gastrointestinal haemorrhage, even fatal, is a common complication in PXE, and constitutes a firm contraindication for the use of aspirin.

In conclusion, there is at present insufficient evidence to postulate an association between PXE and intracranial aneurysms. There is suggestive evidence of a significant association between PXE and ischaemic stroke. The use of aspirin after ischaemic strokes is controversial in this entity in view of frequent gastrointestinal complications.

References

2. Van Soest S, Swart J, Tijmes N, Sandkuijl LA, Rommers J, Bergen AA. A locus for autosomal recessive pseudoxanthoma elasticum, with penetrance of vascular symptoms in carriers, maps to


27. Messis CP, Budzilovich GN. Pseudoxanthoma elasticum, report of an autopsyed case with cerebral


