Combined Inheritance of Purpura Simplex and Ptosis in Four Generations of One Family

By Ben Fisher, Gerald H. Zuckerman and Robert C. Douglass

The hereditary vascular purpuras may be generally grouped into three categories. One group manifests an inconstantly prolonged bleeding time, another is characterized by a normal bleeding time but has a consistently positive capillary fragility test, and the third is associated with localized lesions that predispose to the bleeding tendency. Complete evaluation of the purpura is necessary in each case in order to find the underlying cause, establish some prognostic significance to this finding, and institute a rational means of therapy.

We have had the opportunity to study eleven members of a family—representing four generations—in which capillary fragility is present together with congenital ptosis of the eyelids in six members and alone in one other. The following observations on the inheritance of these two disorders seemed worthy of presentation.

Clinical Study

The proposita (W. T.) is a 60 year old white woman who sought medical attention for fatigue and ankle edema. Because of her history of "easy bruising," spontaneous ecchymoses and hypermenorrhea (before the menopause), a hematologic study was undertaken including pro-thrombin time of plasma and serum and clot retraction at room temperature and 37 C. The only abnormal result was a strongly positive capillary fragility test performed by inflating the sphygmomanometer cuff midway between diastolic and systolic arterial pressures and allowing it to remain for eight minutes. It was also noted that the patient had marked ptosis of her right upper eyelid (fig. 1). No cranial nerve weaknesses could be elicited, and there was no strabismus or nystagmus. Her pupils reacted to light by constriction. On further questioning, we learned that several children and grandchildren of the proposita also had ptosis, prolonged bleeding following dental extractions and they too "bruised easily." The possibility arose, therefore, that genetic transmission of capillary purpura and ptosis might have occurred in this family.

Ten other members of the family were then interviewed. Five were found to have ptosis and positive capillary fragility tests, one had only capillary fragility, one had ptosis alone, and three were normal. Four other persons (in generations IV and V), not available for study, were reported by the proposita and siblings to be normal. The pertinent clinical and hematologic findings are summarized in table 1. Bleeding time determinations (Duke's method) were carefully performed on both ears of several of these persons at periodic intervals to rule out pseudohemophilia,' but were always within normal limits. Platelets were normal in number and appearance on stained films and in wet preparations. In the latter, they acted as foci from which fibrin threads radiated.

With great interest we learned that the mother of the proposita (now deceased) had bilateral ptosis and hypermenorrhea. The eyelid involvement was well demonstrated in an old photograph supplied for us. The genetic relationship of these persons is presented in figure 2.
COMBINED INHERITANCE OF PURPURA SIMPLEX AND PTOSIS

Fig. 1. Photographs illustrating ptosis of the eyelids in three generations. (a) proposita, (b) daughter of proposita, (c) granddaughter of proposita.

DISCUSSION

Classification of the purpura was made by evaluating the hematologic studies and by exclusion of clinical and laboratory features usually found in the other hereditary vascular disorders (table 2). It fits most closely the syndrome that Davis named "hereditary familial purpura simplex." 12

This type of nonthrombocytopenic purpura is believed to be rather mild in its clinical course, but can occasionally give rise to signs such as hypermenorrhea, epistaxis or ecchymosis. 3 While familial occurrence of purpura simplex is supposedly not rare, 3–4 few clinical observations are recorded in the literature, and almost no pedigree of this disorder can be found. It is doubted by some that hereditary familial purpura simplex (established by a positive capillary fragility test as the only abnormal hematologic finding) exists as a true entity. The pedi-
gree listed here helps to reaffirm the familial and hereditary nature of this disorder.

Patients described in the numerous articles concerned with hereditary hemorrhagic diatheses almost always have a prolonged bleeding time. These reports can be found with ease. Regarding purpura simplex, however, most textbooks and papers that include a differential diagnosis of purpura refer only to Davis. Soulier has reported 38 cases of isolated capillary fragility in 490 instances of hemorrhagic disease. Of these, 18 had a familial background. This was a short paper, however, and did not list any pedigrees or individual case records.

The combination of hereditary capillary fragility with congenital and familial ptosis in our family is of interest because of the genetic transmission of each as a dominant trait. The defect in hereditary ptosis is believed to lie in the absence or the faulty development of the levator palpebrae superioris muscle. It is not unusual for this disorder to be associated with other congenital abnormalities.
of the eye or other organs. The most frequent accompanying eye defect is epi-
icanthus; this was observed in only 1 of the persons we studied. The largest
pedigree is that reported by Briggs, listing 23 families which span 6 generations.8

Association of ptosis of the eyelids with a vascular defect has been found only
once in our review of the literature.9 In that instance, however, the vessels in-
volved were the lymphatics of the lower extremities. In this family, the occur-
rence of purpura alone in IV-3 and ptosis alone in V-8 suggests that the two
conditions are inherited in genetic independence of one another, the observed
pattern of transmission suggesting that the traits depend on different dominant
autosomal genes. While the possibility that the two genes in question are lo-
cated on the same chromosome exists, the data are not compatible with close
linkage. An alternate genetic explanation of the findings in this family would
be that both traits comprise a syndrome determined by a single dominant gene
which does not always find full expression. This explanation seems inherently
less likely than the first. No linkage could be demonstrated with the ABO,
MN, or Rh blood group systems.
PTOSIS

<table>
<thead>
<tr>
<th>No.</th>
<th>Status and Name</th>
<th>Age in Years</th>
<th>Sex</th>
<th>Capillary Frailty</th>
<th>Bleeding Time</th>
<th>Ptosis</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mother of Proposita, II</td>
<td>Died at age 65</td>
<td>F</td>
<td>Not examined</td>
<td>3 Min.</td>
<td>+</td>
<td>Bilateral ptosis, death at age 65; hypertension; hypermenorrhea.</td>
</tr>
<tr>
<td>2</td>
<td>Proposita, III</td>
<td>60</td>
<td>F</td>
<td>+++</td>
<td>3 Min.</td>
<td>+</td>
<td>Ptosis of right eyelid; ecchymoses; hypermenorrhea; youngest of 12 children, only one involved according to history.</td>
</tr>
<tr>
<td>3</td>
<td>Daughter of &quot;2,&quot; IV</td>
<td>43</td>
<td>F</td>
<td>+</td>
<td>5 Min.</td>
<td></td>
<td>No ptosis. Bruises easily; ecchymoses; prolonged bleeding from cuts.</td>
</tr>
<tr>
<td>4</td>
<td>Son of &quot;2,&quot; IV</td>
<td>36</td>
<td>M</td>
<td>Not examined</td>
<td></td>
<td></td>
<td>Said to have no ptosis or ecchymoses; has 3 children who are said to be normal.</td>
</tr>
<tr>
<td>5</td>
<td>Daughter of &quot;2,&quot; IV</td>
<td>32</td>
<td>F</td>
<td>+++</td>
<td>5 Min.</td>
<td>+</td>
<td>Bilateral ptosis; ecchymoses; 4 miscarriages; hypermenorrhea; had bleeding into muscles when right leg was fractured.</td>
</tr>
<tr>
<td>6</td>
<td>Son of &quot;2,&quot; IV</td>
<td>27</td>
<td>M</td>
<td>+++</td>
<td>2½ Min.</td>
<td>+</td>
<td>Bruises easily; popliteal ecchymoses; bilateral ptosis.</td>
</tr>
<tr>
<td>7</td>
<td>Son of &quot;5,&quot; V</td>
<td>14</td>
<td>M</td>
<td>++</td>
<td>4 Min.</td>
<td>+</td>
<td>Bilateral ptosis; no bleeding tendency at this time.</td>
</tr>
<tr>
<td>8</td>
<td>Daughter of &quot;5,&quot; V</td>
<td>1 and 1/2</td>
<td>F</td>
<td>Neg.</td>
<td>5 Min.</td>
<td>+</td>
<td>Bilateral ptosis; no ecchymoses.</td>
</tr>
<tr>
<td>9</td>
<td>Son of &quot;6,&quot; V</td>
<td>8</td>
<td>M</td>
<td>+++</td>
<td>3 Min.</td>
<td>+</td>
<td>No ecchymoses.</td>
</tr>
<tr>
<td>10</td>
<td>Son of &quot;6,&quot; V</td>
<td>6</td>
<td>M</td>
<td>Neg.</td>
<td>Not determined</td>
<td></td>
<td>No ptosis or ecchymoses.</td>
</tr>
<tr>
<td>11</td>
<td>Daughter of &quot;6,&quot; V</td>
<td>4</td>
<td>F</td>
<td>Neg.</td>
<td>Not determined</td>
<td></td>
<td>No ptosis or ecchymoses.</td>
</tr>
<tr>
<td>12</td>
<td>Son of &quot;6,&quot; V</td>
<td>2</td>
<td>M</td>
<td>Neg.</td>
<td>Not determined</td>
<td></td>
<td>No ptosis or ecchymoses.</td>
</tr>
<tr>
<td>13</td>
<td>Son of &quot;6,&quot; V</td>
<td>6/12</td>
<td>M</td>
<td>+++</td>
<td>Not determined</td>
<td>+</td>
<td>Bilateral ptosis.</td>
</tr>
</tbody>
</table>

Fig. 2.—Pedigree of family with purpura simplex and ptosis. Numbers under symbols refer to location in Table 1. Shading indicates ptosis; stippling indicates purpura. Vertical lines within the symbols denoting sex-persons examined and found normal. Single horizontal line—person now deceased. Clear symbols—no examination. The diamond denotes siblings of number, age and sex not important in this study. The small completely shaded circle indicates stillbirth, sex unknown.
**Table 2.—Differential Diagnosis of the Hereditary Vascular (Nonthrombocytopenic) Purpuras**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Bleeding Time (Contractility of vessels)</th>
<th>Capillary Fragility Test</th>
<th>Primary Site of Defect</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary familial purpura simplex</td>
<td>Normal</td>
<td>Positive</td>
<td>Capillaries</td>
<td>Purpura in response to minor trauma; epistaxis, ecchymoses, hypermenorrhea; usually no visceral bleeding.</td>
</tr>
<tr>
<td>Pseudohemophilia</td>
<td>Prolonged</td>
<td>Normal</td>
<td>Capillaries (defective contractility when cut)</td>
<td>Typical hemorrhagic diathesis with skin ecchymoses, profuse bleeding after minor trauma or surgery; hypermenorrhea. (Quantitative assay for Antihemophilic globulin reveals subnormal values in certain patients, but higher than in true hemophilia)</td>
</tr>
<tr>
<td>Hereditary hemorrhagic telangiectasia</td>
<td>Normal</td>
<td>Normal</td>
<td>Incomplete wall of vessel at site of telangiectasia</td>
<td>Typical lesions must be present for diagnosis; gastrointestinal tract frequently involved; epistaxis; rarely may be accompanied by pulmonary arteriovenous fistula.</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome</td>
<td>Normal</td>
<td>Normal</td>
<td>Connective tissue of skin (poor anchorage of capillaries)</td>
<td>May present as forme fruste with emphasis on capillary fragility; cutis laxa, hyperextensibility of joints, subcutaneous nodules, papyraceous scars.</td>
</tr>
</tbody>
</table>

**Summary**

Clinical observations are presented on 11 members of a family in which hereditary familial purpura simplex and congenital ptosis coexist in 6. These persons represent 4 generations of dominant genetic transmission of both traits.

**Summario in Interlingua**

Es presentate observationes clinic in re dece-un membros de un familia inter le quales sex ha hereditari purpura simplice familial co-existente con ptosis congenite. Iste personas representa quatro generationes de dominante transmission genetic de ambe ille tractos.

**References**

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