Ectopia lentis et pupillae syndrome in three
generations

J R M Cruysberg, A Pinckers

Abstract
In nine members from three generations and in a distant relative, at least three significant characteristics of the ectopia lentis et pupillae syndrome were established including ectopia lentis, ectopia pupillae, persistent pupillary membrane, iris transillumination, and poor pupillary dilatation. All patients developed bilateral cataract before the age of 40 years, and two patients presented with intermittent acute intraocular hypertensive crises. Not only the high number of patients in one family, but also the occurrence in three generations is very exceptional for the ectopia lentis et pupillae syndrome. Although the syndrome is said to be inherited in an autosomal recessive mode, in this family, a mother to son and a mother to daughter transmission were present. Pedigree analysis yielded arguments in favour of an autosomal dominant inheritance with reduced penetrance. A biochemical correlation was not identified.

Ectopia lentis et pupillae (ELP) is a congenital hereditary disorder in which there is displacement of the lenses and the pupils, associated with other ocular anomalies, but without systemic manifestations. The condition is usually bilateral, with the lenses and pupils displaced in opposite directions. However, a marked variability in expression is observed between the two eyes of a patient and among affected members of a family. The ELP syndrome must be differentiated from displacement of the pupillary position (corectopia) as a result of intraocular surgery, or other progressive ocular disorders – for example, essential iris atrophy, Chandler's syndrome, Rieger's syndrome, and intraocular inflammation.

We examined a patient with classic ELP syndrome and studied the family because the mother of the proposita was also affected.

Patients and methods
The proposita (VII-24), a 36-year-old woman, presenting with congenital bilateral ectopia lentis et pupillae, asked for genetic counselling...
because several members of her family had poor vision. She was diagnosed elsewhere as having Rieger’s syndrome. The patient and her relatives underwent complete ophthalmic examinations, including measurement of the refractive error by subjective techniques (in adults) or cycloplegic retinoscopy (in children). Corrected visual acuity measurement, slit-lamp biomicroscopy of the anterior segment before and after pupillary dilatation, ophthalmoscopy, and applanation tonometry. If ectopia lentis was diagnosed, measurement of the corneal diameter (ruler), corneal curvature (Javal ophthalmometer), and axial length (A scan ultrasonography) were performed. Photographic documentation was performed as previously described. Several members of the family had already been examined in our department. At the time of this study, the two oldest aunts of the proposita were deceased. A genealogical study was performed in order to search for consanguinity between the parents and maternal grandparents of the proposita. Later on, a distant relative (VIII-25) also presented with congenital bilateral ELSP, and the genealogical study was extended. A number of patients underwent elaborate general examinations in order to rule out systemic and metabolic disorders, such as Marfan’s syndrome and homocystinuria.

Results
In one family, we observed 10 patients with a congenital syndrome characterised by bilateral ectopia lentis, and associated abnormalities of the pupil (ectopia pupillae, persistent pupillary membrane, poor pupillary dilatation) and iris (iris transillumination, excentric circular folds). Other ocular complications (cataract, glaucoma, uveitis, retinal detachment), high myopia, and poor vision were also seen. Systemic abnormalities were not found. The family pedigree is shown in Figure 1 and the clinical features are summarised in Tables 1 and 2. The proposita (Figure 2; VII-24), her brother (VII-21), mother (VI-4), a maternal aunt (VI-11), and a distant relative (VIII-25) all had classic ELP syndrome, whereas other family members showed ectopia lentis associated with other major signs of the syndrome. In one case (VI-10), the persistent pupillary membrane was so dense that surgery was needed to open the pupil. All the patients diagnosed as ELSP had a history of poor vision. There was no history of poor vision in the grandparents (V-1 and V-2) of the proposita. The syndrome was present in five patients of generation VI, in three patients of generation VII, and in two patients of generation VIII. One affected female (VI-2) had an affected daughter, whereas another affected female (VI-4) transmitted the trait to a son and a daughter. The spouses of the affected family members, VII-32 and VII-63, were examined and found to be normal.

The maternal grandparents of the proposita were consanguineous. In fact there was consanguinity in three successive generations, but consanguinity of the parents of the proposita could not be demonstrated (Fig 1). The great grandparents, but not the parents of the distant relative (VIII-25), were consanguineous.

None of the affected family members had any systemic abnormalities related to disorders associated with ectopia lentis. In three patients, homocystinuria was ruled out with certainty by serum evaluation in the fasting state and after methionine loading. One patient (VII-10) underwent extensive investigations for metabolic disease: there were no abnormal findings of the amino acids, organic acids, purines, pyrimidines, mucopolysaccharides, oligosaccharides, neuraminic acid, galactitol, and sorbitol in plasma and urine.

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**Table 1** Findings in patients with the ectopia lentis et pupillae syndrome

<table>
<thead>
<tr>
<th>Condition</th>
<th>No of abnormal patients</th>
<th>No. of examined patients</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Ectopia lentis</td>
<td>19/10</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Ectopia pupillae</td>
<td>5/10</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Persistent pupillary membrane</td>
<td>4/9</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Iris transillumination</td>
<td>6/8</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Poor pupillary dilatation</td>
<td>5/10</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>8/8</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Before age 20 years</td>
<td>3/8</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>At age 40 years</td>
<td>8/8</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Glaucoma</td>
<td>7/10</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>4/10</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Uveitis</td>
<td>2/10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Poor vision (&lt;6/20)</td>
<td>18/10</td>
<td>100</td>
<td></td>
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</tbody>
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**Table 2** Clinical findings in the ectopia lentis et pupillae syndrome in affected members of one family
Ectopia lentis et pupillae syndrome in three generations

Figure 2 Patient (VII-24; proposita) with classic ectopia lentis et pupillae syndrome (top), showing upward displaced eccentric pupils (middle), downward displaced subluxated lenses and poor pupillary dilatation (bottom). Only the superior edge of the left lens is visible (arrows).

Discussion

The patients of this study fulfil the criteria for the diagnosis ELP syndrome: in five patients, the characteristic picture of bilateral ectopia lentis with congenital ectopia of oval or slit-shaped pupils was present. In the remaining five patients there were, in addition to bilateral ectopia lentis, a number of symptoms which are described in the studies of the ELP syndrome as significant, such as transillumination of the iris periphery, poor pupillary membrane, poor pupillary dilatation despite repeated pharmacological attempts, high axial myopia, poor vision, a high prevalence of ocular complications at young age – for example, cataract, glaucoma, poor vision, uveitis, retinal detachment, and lack of systemic disorders known to be associated with ectopia lentis.

Other causes of ectopia pupillae were ruled out. Ectopia pupillae simplex (EPS) usually is inherited as an autosomal dominant trait without ectopia lentis. Rieger’s syndrome is characterised by a prominent Schwalbe’s line all around the corneal periphery. There is often hypoplasia of the iris stroma with through and through holes in the iris, causing polycoria and corectopia (ectopia pupillae). Marked corectopia is almost always unilateral in progressive essential iris atrophy, a subtype of the iridocorneal endothelial (ICE) syndrome, which includes disorders of the corneal endothelium with varying degree of endothelialisation of the anterior chamber angle and iris surface.

Ectopia lentis simplex (ELS) is inherited as an autosomal dominant trait, but the existence of an autosomal recessive form also has been reported. Dominantly inherited ectopia lentis simplex is usually bilateral and symmetrical, with the lenses dislocated upward and laterally, but without ectopic pupils.

None of our patients showed clinical signs of Marfan’s syndrome, in which ectopia lentis is commonly present and iris transillumination has been documented clinically. As with ectopia lentis simplex, our patients showed lenticular myopia, amblyopia, cataract, glaucoma, retinal detachment, and poor vision. Compared with other authors, our patients show a remarkably high prevalence of cataract before the age of 40 years. Intermittent acute intraocular hypertensive crises occurred in two affected members of generation VI. Enlarged corneal diameters were not found. Microspherophakia, another symptom sometimes described in the ELP syndrome, was not found.

In some respects the presented family is unique. Ten patients with the ELP syndrome in one pedigree is exceptional. Most pedigrees contain three, sometimes four, and rarely five patients. Because the presence of
ectopic pupils is a selection criterion for the diagnosis of ELP syndrome, the pedigrees with only one affected patient for obvious reasons will show a 100% prevalence of ectopia pupillae. However, many studies show that if there are more patients in one family, ectopia pupillae is not an obligatory sign. In pedigrees with the ELP syndrome, the number of eyes with ectopia lentis presenting with significant ectopia pupillae is near 50%, but may vary from 33% to 100%. The 50% ectopic pupils that we found in our study is in accordance with these data.

Another exceptional finding in our study is the presence of the ELP syndrome in three generations. In ELP pedigrees from the literature (Table 3), the syndrome was present in only one generation in 20 pedigrees. This was also the case in 11 pedigrees published before 1920 and cited by Siemens. ELP is inherited as a recessive trait. François summarised publications from 1885 to 1947 and noted that consanguinity has been reported in many studies. He noted further that there were no exceptions to the concept of an autosomal recessive inheritance. An autosomal recessive inheritance of the ELP syndrome is suggested by the occurrence in several siblings of one generation, consanguinity, and an equal distribution between males and females. Extensive search of the literature resulted in only two pedigrees with the ELP syndrome, the number of cases, have a common genetic origin. Whatever the transmission, the affected members of the pedigree we present here are suffering from a common genetic defect.

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2 Waardenburg PJ. Over het erfelijkheidsmoment bij de angeboren verplaatting van de pupil en lens. Genetica 1924; 6: 337-82.