Combined granular lattice dystrophy (Avellino corneal dystrophy)

EDITOR,—Lattice type 1 and granular corneal dystrophies are considered to be distinctive, both clinically and histologically. There have been several recent family studies in which patients with features of combined lattice type 1 and granular dystrophy were described.1-3 Apart from one family,4 all of the cases reported to date have ancestral origin in the Italian province of Avellino. In this report, we present the clinical and pathological findings in a 54-year-old Irish woman with such a combined dystrophy. This woman is of indigenous Irish extraction and has no history of Italian ancestry. The findings in this patient lend support to the hypothesis that granular dystrophy and lattice type 1 dystrophy may be phenotypic variations caused by mutations in the same gene. Granular, lattice type 1 and Avellino dystrophies have been independently linked to the same region on chromosome 5q by genetic linkage analysis.6

CASE REPORT
A 54-year-old woman presented to the Anterior Segment Clinic at the Royal Victoria Eye and Ear Hospital, Dublin, in 1978 with bilateral sore eyes. On slit-lamp examination, she was found to have discrete, crumb-like, grey-white deposits in the anterior axial corneal stroma. Clear areas were present between the deposits. Her vision was 6/12 bilaterally. A diagnosis of granular dystrophy was made. Her family history was negative for visual problems, including her two deceased half siblings and three children. A detailed family history revealed that all family members were of indigenous Irish origin. There was no history of Italian ancestry. Over the next few years she had several episodes of photophobia and decreased vision with, on examination, keratitis and punctate fluorescein staining. In 1988, slit-lamp examination at the Corneal Clinic revealed lattice-like changes in addition to the typical findings of granular dystrophy, with a characteristic stromal haze detected between the typical granular deposits. Figure 1 illustrates the corneal changes in 1993 before left penetrating keratoplasty carried out because of recurrent corneal erosions associated with bulla formation.

Pathological findings
Histological examination of the left corneal button revealed epithelial oedema with central bullous keratopathy and partial loss of Bowman's layer. Many rectangular eosinophilic deposits were present in the mid and deep corneal stroma. These stained bright red on Masson's trichrome staining (Fig 2a). A linear subepithelial deposit also stained bright red with Masson's trichrome stain. The deposits showed no reaction with periodic acid Schiff or acid mucopolysaccharide methods, thus fulfilling the criteria for a diagnosis of granular dystrophy.7 In addition, weakly fuchsinophilic fusiform deposits were noted in the superficial and deep stroma. These deposits stained orange with congo red and had intense apple green dichroism in polarised light. These latter findings are diagnostic of amyloid. Some of the granular type deposits also showed focal areas of apple green birefringence (Fig 2b) and were partially positive with congo red. Descemet's membrane was intact and of normal thickness. There were 11 endothelial nuclei per high power field. Examination of the cornea by transmission electron microscopy (Fig 2d) revealed abundant extracellular electron dense 80-100 nm filaments, typical of amyloid, present throughout the stroma. Rectangular electron dense deposits which could represent granular deposits or transitional structures were also seen (Fig 2c).

Immunohistochemical studies for kappa and lambda light chains and for cytokeratin were negative. These studies were performed on formalin fixed and paraffin embedded sections using monoclonal antibodies (Dako, Copenhagen, Denmark) and an avidin biotin peroxidase kit (Vector Labs, Burlingame, CA, USA).

Table 1 Comparison of lattice dystrophy and granular dystrophy

<table>
<thead>
<tr>
<th>Lattice (type 1)</th>
<th>Granular</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomicroscopic appearance</strong></td>
<td>Thin central arborising linear opacities in the superficial stroma</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>Subepithelial and stromal deposits of amyloid Congo red positive, autofluorescent and birefringent</td>
</tr>
<tr>
<td><strong>Inheritance</strong></td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td><strong>Ultrastructure</strong></td>
<td>Fine non-branching 80–100 nm filaments</td>
</tr>
</tbody>
</table>

Figure 2 (a) Photomicrograph of a histological section stained with Masson trichrome demonstrating rectangular fuchsinophilic stromal deposits, typical of granular dystrophy (magnification ×120). (b) Photomicrograph of parallel histological section stained with Congo red and photographed under polarised light to demonstrate birefringence typical of amyloid (magnification ×120). (c) Electron micrograph illustrating variably electron-dense rectangular filamentous deposits which resemble those described in granular dystrophy. These may represent structures transitional between granular and lattice dystrophy (magnification 18 000). (d) Electron micrograph illustrating electron dense extracellular, non-branching 80–100 nm filaments, typical of amyloid, in the corneal stroma (magnification 108 000).
Amyloidosis is a localised or systemic disorder in which there is abnormal extracellular deposition of protein fibrils associated with sulphated glycosaminoglycans and serum amyloid P. The fibrils may be formed from a variety of precursor proteins including immunoglobulin light chains and keratin. The nature of corneal amyloid is currently unknown. Our studies confirm that immunoglobulin light chains and keratin are not present in corneal amyloid.

It has been suggested that microfibrillar proteins in deposits of granular dystrophy. The protein gelsolin has been found by immunohistochemistry in both granular dystrophy and lattice dystrophy, type 1. It is possible that some cases of lattice dystrophy and granular dystrophy may share another as yet unidentified microfibrillar protein. There have been reports of patients with lattice-like changes in otherwise typical granular dystrophy and reports of granular deposits in families with clinical lattice dystrophy. Recently, amyloid deposition has been documented in association with granular dystrophy in families with ancestral origin from the Italian province of Avellino. It has been suggested that this combined dystrophy is due to a variation of granular dystrophy involving deposition of lattice-like amyloid deposits. These cases have been termed granular lattice (Avellino) corneal dystrophy.

Gene linkage studies have found that Avellino type combined dystrophy, lattice type 1 dystrophy, and granular dystrophy share the same locus on the long arm of chromosome 5. One of the families with Avellino type dystrophy, which had no Italian heritage, did not have the same alleles as the Italian families at the chromosome 5 locus. This suggests that a different mutation has given rise to the dystrophy in that family. The patient reported here has no history of Italian heritage. Presumably, an independent mutation has caused her dystrophy. This case lends further weight to the emerging genetic and clinical information that granular and lattice dystrophies may represent differing phenotypic expressions of the same disease and that combined cases may be more frequent than has been generally appreciated.

CASE REPORTS

Case 1

The index case, a girl, was the second child of healthy unrelated parents. She was noted at birth to have dolicocephaly, clinodactyly of the fifth fingers, and apparent hypertelorism. Subsequently she was noted to develop other clinical features of CED, including sagittal suture synostosis, short narrow thorax secondary to rib abnormalities, short limbs, short digits, single palmar creases, short thin hair, small teeth, and short nails (Fig 1). As an infant, she suffered recurrent chest infections and bronchospasm, at one stage requiring ventilation. She developed fits at age 3 years that were not satisfactorily controlled with sodium valproate. Elevated serum creatinine was noted when she was aged 4 years: chronic renal failure due to tubulointerstitial nephropathy was to reach a fatal end stage shortly before her sixth birthday.

From the age of 18 months her mother noticed that she had difficulty with distance vision. Ocular examination at age 2 years demonstrated 4/50 DS myopia for which spectacles were prescribed, but no other abnormality was found. In her third year of life she began to have difficulty navigating in dim illumination, walking with arms outstretched to avoid unseen obstacles. When examined at age 4 years the visual acuity was 6/36 with an unchanged myopic correction, and fundus examination was normal. However, electroretinography using skin electrodes demonstrated a grossly reduced scotopic response ('b' wave amplitude 8 µV both eyes: normal minimum 20 µV), and a moderately reduced photopic response ('b' wave amplitude 3-2-4 µV right, 5-6 µV left: normal minimum 5 µV) with critical flicker fusion reduced at 20 Hz for both eyes. Flash visual evoked response showed normal latency from each eye but reduced amplitude on the right. A year later she was symptomatically stable, and visual acuity and electrodiagnostic findings showed no significant change.

Case 2

The younger brother of case 1 exhibited clinical findings very similar to those of his sister (Fig 1). In addition to the features of CED, he too had multiple chest infections and evidence of renal failure. At 18 months he was found to have vertical palpebral nystagmus and moderate hypermetropic astigmatism (+2-00 DC both eyes). Funduscopy showed normal discs, vessels, and retina. Despite corrective spectacles, Snellen acuity remained poor at 6/18 and the child complained that he could not see in dim lighting conditions. When aged 4 years, skin electrode electroretinography showed grossly reduced amplitude of both photopic and scotopic 'a' and 'b' waves, with no consistent flier response. When last reviewed at age 5 years, visual acuity was unchanged, and funduscopy showed normal discs and vessels with a slightly granular appearance of the mid-peripheral retina.

COMMENT

The cranioskeletal and ectodermal findings in these siblings are typical of those associated with cranioectodermal dysplasia (CED), a rare autosomal recessive condition with characteristic craniofacial, skeletal, and ectodermal abnormalities. These include dolicocephaly (long skull), which is usually associated with sagittal suture synostosis, frontal bossing with hypertelorism, high arched palate, short narrow thorax, short limbs, and short stubby digits. Ectodermal manifestations include short nails, fine sparse slow growing hair, and small widely spaced teeth. Less frequent associations are cardiac valvar abnormalities, recurrent chest infections, and apparent hepatosplenomegaly as a result of the small thorax. Intelligence is normal.

Ophthalmic features which have been noted previously include hypertelorism, marked epicantic folds, hyperopia, myopia, and nystagmus. We now provide further details of two previously described siblings both of whom have developed a symptomatic photoreceptor dystrophy and chronic renal failure.

A new oculorenal syndrome: retinal dystrophy and tubulointerstitial nephropathy in cranioectodermal dysplasia

EDITORS—Cranioectodermal dysplasia (CED) is a rare autosomal recessive condition with characteristic craniofacial, skeletal, and ectodermal abnormalities. These include dolicocephaly (long skull), which is usually associated with sagittal suture synostosis, frontal bossing with hypertelorism, high arched palate, short narrow thorax, short limbs, and short stubby digits. Ectodermal manifestations include short nails, fine sparse slow growing hair, and small widely spaced teeth. Less frequent associations are cardiac valvar abnormalities, recurrent chest infections, and apparent hepatosplenomegaly as a result of the small thorax. Intelligence is normal.

Ophthalmic features which have been noted previously include hypertelorism, marked epicantic folds, hyperopia, myopia, and nystagmus. We now provide further details of two previously described siblings both of whom have developed a symptomatic photoreceptor dystrophy and chronic renal failure.

The younger brother of case 1 exhibited clinical findings very similar to those of his sister (Fig 1). In addition to the features of CED, he too had multiple chest infections and evidence of renal failure. At 18 months he was found to have vertical palpebral nystagmus and moderate hypermetropic astigmatism (+2-00 DC both eyes). Funduscopy showed normal discs, vessels, and retina. Despite corrective spectacles, Snellen acuity remained poor at 6/18 and the child complained that he could not see in dim lighting conditions. When aged 4 years, skin electrode electroretinography showed grossly reduced amplitude of both photopic and scotopic 'a' and 'b' waves, with no consistent flier response. When last reviewed at age 5 years, visual acuity was unchanged, and funduscopy showed normal discs and vessels with a slightly granular appearance of the mid-peripheral retina.

COMMENT

The cranioskeletal and ectodermal findings in these siblings are typical of those associated with cranioectodermal dysplasia (CED), a rare autosomal recessive condition with characteristic craniofacial, skeletal, and ectodermal abnormalities. These include dolicocephaly (long skull), which is usually associated with sagittal suture synostosis, frontal bossing with hypertelorism, high arched palate, short narrow thorax, short limbs, and short stubby digits. Ectodermal manifestations include short nails, fine sparse slow growing hair, and small widely spaced teeth. Less frequent associations are cardiac valvar abnormalities, recurrent chest infections, and apparent hepatosplenomegaly as a result of the small thorax. Intelligence is normal.

Ophthalmic features which have been noted previously include hypertelorism, marked epicantic folds, hyperopia, myopia, and nystagmus. We now provide further details of two previously described siblings both of whom have developed a symptomatic photoreceptor dystrophy and chronic renal failure.

The younger brother of case 1 exhibited clinical findings very similar to those of his sister (Fig 1). In addition to the features of CED, he too had multiple chest infections and evidence of renal failure. At 18 months he was found to have vertical palpebral nystagmus and moderate hypermetropic astigmatism (+2-00 DC both eyes). Funduscopy showed normal discs, vessels, and retina. Despite corrective spectacles, Snellen acuity remained poor at 6/18 and the child complained that he could not see in dim lighting conditions. When aged 4 years, skin electrode electroretinography showed grossly reduced amplitude of both photopic and scotopic 'a' and 'b' waves, with no consistent flier response. When last reviewed at age 5 years, visual acuity was unchanged, and funduscopy showed normal discs and vessels with a slightly granular appearance of the mid-peripheral retina.