The eye in the CHARGE association

I M Russell-Eggitt, K D Blake, D S I Taylor, R K H Wyse

Abstract

CHARGE association includes patients with at least four features prefixed by the letters of the mnemonic: Coloboma, Heart defects, Atresia of the choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies and/or hearing loss. Many also have facial palsy. We report a series identified by collaboration within one centre of all specialties concerned in the management of the CHARGE association. Ocular abnormalities were found in 44 out of 50 patients with the CHARGE association. Of these, 41 had 'typical' colobomata. The majority had retinochoroidal colobomata with optic nerve involvement, but only 13 patients had an iris defect. Two patients had atypical iris colobomata with normal fundi. Additional features were microphthalmos in 21 patients, optic nerve hypoplasia in four, nystagmus in 12, and a vertical disorder of eye movement in four of the 22 cases with facial palsy. We report an incidence of coloboma in the CHARGE association of 86% (43/50) compared with a previous cumulative reported incidence of 66% (112/170). We believe that there may have been previous underdiagnosis of colobomata in children with multiple congenital abnormalities.

Among the myriad of congenital abnormalities seen in paediatric practice the grouping of cases where certain features often occur in association is useful and often precedes understanding of the aetiology.

The CHARGE association includes patients with at least four features prefixed by the letters of the mnemonic: Coloboma, Heart defects, Atresia of the choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies and/or hearing loss.¹ The diagnosis has become more specific as patients with this phenotype but with a known aetiology, such as cat-eye syndrome (partial tetrasomy 22), Di-George syndrome (deletion 22q11), and multiple abnormalities due to teratogens such as retinoic acid, are excluded.

Most cases of CHARGE seem to be sporadic. Environmental or genetic causes may act similarly. Autosomal dominant pedigrees of CHARGE give support to a genetic basis in a minority of patients.²⁻⁵ The similarities between patients are striking, and there is considerable concordance within dominant pedigrees. In 1981 Pagon *et al*¹ described this non-random series of features comprising CHARGE association in order that later splitting by aetiology might be possible. Since then it has become clear that facial palsy, renal abnormalities, orofacial clefts, and tracheo-oesophageal fistulae also frequently accompany the main features.⁶

Warburg has suggested that the VACTERL

association (vertebral malformation, atresia of the anus, cardiac malformation, tracheal fistula, oesophageal atresia, renal and radial dysplasia, and limb malformations) may be an expression of the same defect as the CHARGE association.⁷

Pagon *et al*¹ and subsequently several other authors⁸⁻⁹ have included in the CHARGE association cases of the Di-George syndrome. This is a disorder in development of the third and fourth pharyngeal pouches, with parathyroid and thymic hypoplasia, cleft palate, micrognathia, low-set ears, and heart defects,¹⁰ now known sometimes to be due to a deletion in the region 22q11 of chromosome 22.

Davenport *et al*¹¹ reported a series of 15 patients with the CHARGE association, with a similar multidisciplinary ascertainment to our study. In many other reports of the CHARGE association there is a bias towards certain abnormalities: the 17 cases described by Hall were selected on the basis of choanal atresia and multiple abnormalities.¹² Pagon *et al*¹ described 21 patients all of whom had choanal atresia and/or colobomata. In the most recent review of the CHARGE association Chestler and France¹³ added six further cases with a bias towards colobomata.

In this paper we report the incidence and range of ocular features in the CHARGE association. Our aim was to record the largest series to date and to reduce bias of ascertainment by collaboration, within one centre, of all specialties concerned in the management of the CHARGE association.

Patients and methods

This study describes the ophthalmic features of 50 patients with the CHARGE association all of whom have been seen at one centre. Ascertainment of patients, both retrospective and prospective, was through a variety of specialists: a general paediatrician, geneticist, cardiologist, otorhinolaryngologist, and ophthalmologist. Most cases presented as neonates requiring major surgery for congenital heart disease, choanal atresia, or tracheo-oesophageal fistula. Patients with CHARGE features were screened during this study, if not previously, by all the specialists for further features. The minimum criterion for inclusion in our study required that patients should have at least four of the major features in the acronym.¹¹ There were 28 males and 22 females. There were 13 deaths, most during the first year of life; those who died had all undergone at least three non-ophthalmic surgical procedures.

The six major systemic features of CHARGE are presented in Table I. Facial palsy was also included as a major feature, as it has been previously reported in at least 40 cases and is an otherwise uncommon finding in infancy.¹⁴

Department of Ophthalmology, Hospital for Sick Children, Great Ormond Street, London
I M Russell-Eggitt
D S I Taylor

Department of Paediatric Cardiology, Institute of Child Health, 30 Guilford Street, London WC1
K D Blake
R K H Wyse

Correspondence to:
D S I Taylor, FRCP, FRCS,
Hospital for Sick Children,
Great Ormond Street, London
WC1N 3JH.

Accepted for publication
26 January 1990

TABLE I The initial letters of the acronym CHARGE are used to denote features present in each case reported

Coloboma	
Heart defect	
Atresia of choanae	
Retardation of growth or development	
Genital hypoplasia	
Ear abnormalities or deafness	
palsy of facial nerve	
1 CHARGEp	26 H RGEp
2 CHARGE	27* CHAR E
3* C AR Ep	28 CHARGEp
4* CHAR E	29 CH RGE
5 CHARGEp	30 CH RGE
6 C RGE	31* CHAR Ep
7 CH R Ep	32* CH R Ep
8 CH RGE	33* C AR E
9 CH RGEp	34 CH RGE
10 CHA GEp	35 CH RGEp
11 HARGE	36* CHAR Ep
12* CHA E	37* CHAR Ep
13 CHA GEp	38* CHAR E
14 C RGEp	39 CH RGEp
15 CHARGE	40* CH R E
16* CHAR E	41 H RGEp
17 CHARGEp	42* CH R E
18 C ARGE	43 CH RGE
19* CHAR Ep	44* CH R E
20* CHAR Ep	45* HAR E
21 CH RGEp	46* HAR E
22 CHARGE	47* CH R E
23* HAR E	48 CH RGE
24* CHAR Ep	49 CH RGE
25 CHARGE	50* C AR E

*Denotes female.

Genital abnormalities were apparent only in the males.

Results

KARYOTYPES

Chromosome analysis was performed in 48/50 of the patients and an abnormality in blood chromosomes was confirmed only in case 36, which had an apparently balanced translocation of chromosomes 6 and 8.

OCULAR FINDINGS

The ocular features of the individual patients are summarised in Table II. Ocular abnormalities were found in 44/50 patients (88%); 41 (82%) of these had a 'typical' coloboma of varying severity. Two patients had atypical iris colobomata with normal fundi: case 8 had a unilateral upper nasal defect and case 48 had bilateral nasal defects.

Figure 1: The right optic disc of case 50 has a hyperpigmented border, the visual acuity is 6/6 with a -3.00 dioptre sphere. The fellow optic disc is colobomatous with inferonasal chorioretinal thinning and scleral ectasia. The acuity is 6/36 with -12.00 dioptre sphere.

Figure 1A

TABLE II The frequency of occurrence of major ocular features is tabulated

	Number of patients			
	Right	Left	Bilateral	Total
Colobomata				
Iris	5	2	6	13
Retinochoroidal	7	3	30	40
Optic disc	4	6	27	37
Eyelid				1
Microphthalmos	7	6	8	21
Squint				17
Nystagmus				12

Colobomata affected the posterior segment in 38/50 cases (bilateral in 32). Two additional cases had gross microphthalmos of the fellow eye, and in all but seven eyes the optic disc was involved.

In some cases the coloboma was very subtle, but nonetheless of diagnostic importance: three patients had iris colobomata which involved only part of the stroma, and two patients with posterior colobomata had only a small defect in the retinal pigment epithelium just below and nasal to the optic disc. The optic disc in these patients had a hyperpigmented border, especially temporally, and in one eye this was the only abnormality, but the fellow eye had a disc coloboma with inferonasal chorioretinal thinning with scleral ectasia (Figs 1A, 1B).

Microphthalmos was bilateral in eight patients, right sided in seven, and left in six, but was mild in the majority. Only one eye of three patients had no useful vision.

Optic nerve hypoplasia was noted in patients 19, 30, 41, and 50. In all these cases the eye with the hypoplastic disc was the better seeing eye, with an acuity range of 6/6-6/18. Only patient 50 had a pigmented optic disc border, and none had the double pigmented ring sign of optic nerve hypoplasia.

Two patients (17 and 41) had unilateral persistent hyperplastic primary vitreous (without a fundal view), case 17 had a 'typical' coloboma (that is, occurring along the embryonic fissure), while case 41 had hypoplasia of the fellow optic disc. Patient 47 had partial upper lid colobomata, and two cases (9 and 47) had blockage of the nasolacrimal duct.

One patient (18) had cataract in association with retinal detachment, and case 17 had spon-

Figure 1B

Figure 2: The right eye of case 19 fails to elevate fully, especially in adduction, and the left eye shows apparent overaction in laevoversion. The left eye is mildly microphthalmic, with inferior corneal scarring due to facial nerve weakness.

taneous dislocation of the lens. In case 25 there was a unilateral anterior polar lens opacity. Strabismus was present in 17 patients: seven esodeviations, eight exodeviations, and two which were initially convergent but became divergent.

Nystagmus was seen in 14 (28%). All of these had optic disc colobomata except for case 7, which had pallor of the retinal pigment epithelium only inferonasal to normal optic discs. The nystagmus was horizontal except in cases 2, 27, and 49. In cases 2 and 27 it was rotary, with profound hearing loss also present, while in case 49 the eye movements were initially chaotic, later settling, with bursts of vertical nystagmus.

In four cases (5, 9, 19, and 39) there was a disorder of vertical eye movement associated with facial palsy, with deficiency of upgaze, particularly in adduction, of the eye contralateral to the facial nerve weakness (Fig 2). Facial palsy was present at birth or noted soon afterwards in 22 cases (13 right, seven left, and two bilateral). One additional patient, case 3, had hemifacial spasm which resolved. Twenty-one of our patients with facial palsy had a strong Bell's reflex and copious tear formation. Cases 5, 35, and 49 had corneal exposure, with scarring, requiring lateral tarsorrhaphy in spite of simple eye ointment application.

Case 7 had a saccade palsy or oculomotor apraxia, and case 5 had a jaw winking ptosis of Marcus-Gunn type. Cases 1, 19, 32, and 39 had narrow palpebral apertures ipsilateral to microphthalmos. Case 27 had bilateral asymmetrical ptosis, normal sized eyes, and poor levator function which required an internal sling operation on the worse affected side.

Patients 10, 12, 20, 29, 32, 36, and 49 were initially thought to be blind, with no apparent fixing or following, and 'chaotic' eye movements. In all these cases there were bilateral optic disc and extensive chorioretinal colobomata. All

these patients improved in visual behaviour. Nystagmus developed in patients 12, 20, and 49.

Thirty-six patients had their refraction estimated. Of these 19 were myopic, eight were hypermetropic, nine were emmetropic, and 14 had more than 2 dioptres of astigmatism. The Snellen acuity was recorded in only 12 cases, the remainder being too young or mentally retarded. One patient had an acuity of 2/60, and another had 2/36 in the better eye; the remainder of patients ranged from 6/5 to 6/18 in their better eyes. There was no correlation between the severity of ocular defect and mental handicap. A more severe visual defect, even absence of light perception, was suspected in some patients with optic disc colobomata.

Discussion

The major ocular feature of the CHARGE association is coloboma. The reported incidence is influenced both by ascertainment and by examination (most colobomata affect the posterior segment alone and some may be subtle defects). We report an incidence of 86% (43/50) compared with a previous cumulative reported incidence of 66% (112/170).^{1-8 11-13 15-24} In some studies not all cases were examined by an ophthalmologist, and as posterior colobomata often occur without an iris defect (30/50 in our series) they may have been under-reported. Subtle defects in the retinal pigment epithelium or iris transillumination defects along the presumptive line of the fetal fissure accounted for five of our cases and could easily have been overlooked if colobomatous defects were not being specifically sought.

In our series a grossly hyperpigmented optic disc border was observed both with and without hypopigmented retinal pigment epithelium (cases 38 and 50). This hypopigmentation occurred along the presumptive line of the embryonic

fissure. In case 50 the fellow eye had a typical disc coloboma (Fig 1). Such an optic disc appearance has been described previously in a family with microphthalmos and clinical anophthalmos, but without typical coloboma.²⁵ As microphthalmos is acknowledged as being often associated with coloboma, this adds to the case for 'hyperpigmented optic disc border' sharing a similar aetiology. The peripapillary hyperpigmentation observed in our patients may be associated with anomalous closure of the superior end of the fetal fissure.

The majority of colobomata in our series were typical in that they were fetal fissure defects. In the embryo during the invagination of the optic vesicle a groove (the embryonic fissure) remains open at the inferior aspect of the optic cup, allowing entry of paraxial mesoderm which later forms the hyaloid system. At 4–5 weeks the fissure begins to close centrally, with apposition extending anteriorly and posteriorly by 6 weeks. We observed the complete spectrum of defects previously described,^{1,3,11,13} encompassing iris to chorioretinal coloboma with or without optic disc involvement and microphthalmos. Visual acuity ranged in our series from light perception to 6/5 Snellen.

Horizontal pendular nystagmus in the CHARGE association in two of six cases with colobomata has been reported by Chestler and France.¹³ In these cases it may be secondary to macular or optic nerve involvement in a coloboma. We propose that nystagmus may also be central in origin. We found our case 7 to have horizontal nystagmus, no major eye defect, and inner ear abnormalities. Furthermore, we found vertical or rotary nystagmus in three patients.

We describe a vertical disorder of eye movement in 4/22 cases with facial palsy, characterised by defective elevation of the globe, with the characteristics of either 'superior oblique muscle overaction' or, in one case, of 'superior rectus underaction'. Traction test has not been possible in all cases to exclude a mechanical limitation of globe movement. However, central disorders of ocular motility are not unexpected in a syndrome in which congenital facial palsy and disorders of swallowing are major features. Vocal cord paralysis has also been reported.¹⁵

Few cases of ptosis have been reported in the CHARGE syndrome, and most of these are probably pseudoptoses associated with microphthalmos or orbital asymmetry.^{16,22,24} Patient 27, with true ptosis, phenotypically resembled Turner's syndrome but had normal chromosomes. August *et al*²² reported one case of ptosis which may have been central in origin and who also had a disorder of eye movement, but no mention of ocular size was made.

Facial palsy has been previously reported in the CHARGE association,¹¹ but as we add a large number of cases, 22/50 (44%), it may be arguably included as one of the major diagnostic features.

Delayed visual maturation (DVM) has been reported in infants who are severely ill from various causes, including tracheo-oesophageal fistula and chest infection,²⁶ and in cases with an ocular disorder such as cataracts,²⁶ albinism,²⁷ and retinal coloboma.¹¹ Seven of our patients had

DVM and all had bilateral optic disc and chorioretinal colobomata. All required major surgery as neonates; two of them had tracheo-oesophageal fistula, two had laryngomalacia and Nissen's fundoplication.

Our two cases of atypical iris coloboma occurred without posterior segment coloboma. This supports the view that these are not related to a defect in closure of the fetal fissure. François²⁸ considered them to be a partial aniridia due to a notch at the margin of the optic vesicle.

Case 47 had notches between the inner third and outer two-thirds of the margin of the upper eyelid. This has not been previously reported in the CHARGE association. Other reported cases of lid coloboma^{18,20} do not offer sufficient clinical information to determine whether patients had the CHARGE phenotype. Upper lid colobomata are a well described feature of the Goldenhar-Gorlin syndrome,²⁹ while lower lid defects occur in the Treacher Collins syndrome.³⁰

Persistent hyperplastic primary vitreous, seen in two of our cases, has been described in association with coloboma in trisomy 13,²⁷ which shares many other features with CHARGE.

In the present series as in cases reported elsewhere there is a notable absence of other ocular abnormalities, such as anterior segment dysgenesis and primary cataracts (only case 25 had a primary lens opacity).

Ho *et al*²⁴ described a mother and her two children with cataract, but they had only 'CH' of CHARGE, and the pregnancy was complicated by diabetes. Their case 5 may have had CHARGE with cataract, as did case II-1 reported by Davenport *et al*,¹¹ though this patient may have had cataract secondary to retinal detachment. Retinal detachment has been reported in association with posterior colobomata and aphakia in patients with the CHARGE association.^{4,11} This emphasises the need for specialist initial eye examination with regular follow-up.

We excluded one patient from our series who had facial palsy and all of the acronymous features of the CHARGE association except for choanal atresia, as chromosome analysis showed him to be trisomic for a part of chromosome 22: the cat-eye syndrome. The phenotypes of the

TABLE III The phenotypes of syndromes which resemble CHARGE association are tabulated with, where possible, an indication of the frequency of occurrence of individual features

	C	H	A	R	G	E
	C ¹²⁻¹⁴	A	T	E	Y	E
	G ^{29,35}	O	L	D	V ^{36,37}	I
	D	E	N	H	A	R
	E	R	L	E	G	S
Heart defect	***	***	*	***	***	***
Ear anomaly	***	***	***	*	***	***
Coloboma	***	***	*		*	**
Atresia choanae	***	**		*		
Genital anomaly	**		*	*	R	***
Retardation	**	*	*			***
Cleft lip/palate	*	*	*	*	*	*
Renal anomaly	*	***	*	**	*	*
Vertebral anomaly	*	*	**	**	*	*
Anal atresia	*	**		**		*
Thymus deficient		R			***	*

***Very often (>50%).

**Often (>30%).

*Occasional (>5%).

R=Reported.

TABLE IV Reported ocular features in syndromes with systemic features in common with the CHARGE association

	C ²⁹	C ³²	G ²⁹ O L	V ³⁹	D ¹ I	E ³⁸
	C	A	D	A	G	D
	H	T	E	C	E	W
	A		N	T	O	A
	R	E	H	E	R	R
	G	Y	A	R	G	D
	E	E	R	L	E	S
Coloboma	*	*	*		*	*
PHPV	*					
Epibulbar dermoids			*			
Lid coloboma	*		*			
Ocular motility disorder	*		*			
Optic nerve hypoplasia	*		*			

cat-eye syndrome and the CHARGE association are remarkably similar (see Table III). Some patients reported as CHARGE (including some in our series) may be mosaics for cat-eye or have a small deletion of chromosome 22 as in Di-George syndrome. Mosaics with normal blood chromosomes have been reported in full trisomy 22,³¹ the abnormality being only detected on fibroblast culture.

Our case 36 with an apparently balanced translocation may provide the cytogenetic clue leading to the identification of a submicroscopic deletion which could be the cause of other cases at present diagnosed as having the CHARGE syndrome with overtly normal chromosomes.

Ocular features may help to separate the different phenotypes of Di-George, VACTERL, cat-eye, and Goldenhar-Gorlin syndromes which have systemic characteristics in common with CHARGE (see Tables III and IV).

CONCLUSIONS

In a large series with the CHARGE association, we have described the spectrum of coloboma-microphthalmos including subtle defects such as a pallor of the retinal pigment epithelium inferonasal to the optic disc and marked peripapillary pigmentation. Ocular motility disorders of central origin also occur frequently; nystagmus may be horizontal, vertical, or rotary. Facial nerve palsy may be accompanied by a vertical ocular deviation.

Colobomata of the posterior segment with associated retinal detachment may be present without iris defect (30/50 had a coloboma of the posterior segment with normal irides). A large chorioretinal coloboma even with involvement of the optic disc may be consistent with moderately good central vision, but a superior visual field defect is to be expected. Refractive errors are common. Twelve of our patients have benefited from spectacles, and there may be ocular morbidity due to both meridional and strabismic amblyopia.

It is important for paediatricians to be aware of the ophthalmic features of the CHARGE association, since some, such as choroidoretinal coloboma, may be occult until complicated by retinal detachment. Ophthalmologists should be aware of the potential systemic associations of coloboma. Patients do not necessarily present as

sick neonates to specialist centres; a few may be diagnosed later in life.

While the finding of typical colobomata is not specific to the CHARGE syndrome, additional findings such as facial nerve palsy may point to this diagnosis in a child with multiple abnormalities. We add a description of a dysplastic optic disc with marked peripapillary pigmentation. In addition two patients had atypical iris colobomata with normal fundi, while another had upper eyelid colobomata.

1 Pagon RA, Graham JM, Zonana J, Yong S-L. Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr* 1981; **99**: 223-7.

2 Kaplan LC. Choanal atresia and its associated anomalies. Further support for the CHARGE association. *Int J Pediatr Otorhinolaryngol* 1985; **8**: 237-42.

3 Hittner HM, Hirsch NJ, Kreh GM, Rudolf AJ. Colobomatous microphthalmos, heart disease, hearing loss, and mental retardation - a syndrome. *J Pediatr Ophthalmol Strabismus* 1979; **16**: 122-8.

4 Mitchell JA, Giangiacomo J, Hefner MA, Thelin JW, Pickens JM. Dominant CHARGE association. *Ophthalmic Paediatr Genet* 1985; **6**: 31-6.

5 Metlay LA, Smythe PS, Miller ME. Familial CHARGE syndrome: clinical report with autopsy findings. *Am J Med Genet* 1987; **26**: 577-81.

6 Oley CA, Baraitser M, Grant DB. A reappraisal of the CHARGE association. *J Med Genet* 1988; **25**: 147-56.

7 Warburg M. Ocular coloboma and multiple congenital anomalies: the CHARGE association. *Ophthalmic Paediatr Genet* 1983; **2**: 189-99.

8 Stewart G, Young DG, Azmy AF. CHARGE association in neonates presenting with choanal atresia. *Z Kinderchir* 1987; **42**: 12-3.

9 Brown OE, Burns DK, Smith TH, Rutledge JC. Bilateral posterior choanal atresia: a morphologic and histologic study, and computed tomographic correlation. *Int J Pediatr Otorhinolaryngol* 1987; **13**: 125-42.

10 Rohn RD, Leffell MS, Leaden P, Johnson D, Rubio T, Emanuel BS. Familial third-fourth pharyngeal pouch syndrome with apparent autosomal dominant transmission. *J Pediatr* 1984; **105**: 47-51.

11 Davenport SLH, Hefner MA, Mitchell JA. The spectrum of clinical features in CHARGE syndrome. *Clin Genet* 1986; **29**: 298-310.

12 Hall BD. Choanal atresia and associated multiple anomalies. *J Pediatr* 1979; **95**: 395-8.

13 Chestler RJ, France TD. Ocular findings in CHARGE syndrome. *Ophthalmology* 1988; **95**: 1613-9.

14 Bergstrom L. Syndromes associated with congenital facial paralysis. *Otolaryngol Head Neck Surg* 1981; **89**: 336-42.

15 Lin AE, Chin AJ, Devine W, Park SC, Zackai E. The pattern of cardiovascular malformation in the CHARGE association. *Am J Dis Child* 1987; **141**: 1010-3.

16 Goldson E, Smith AC, Stewart JM. The CHARGE association: how well do they do? *Am J Dis Child* 1986; **140**: 918-21.

17 Pardo JM, Chua C. The CHARGE association in a male newborn infant. *Clin Pediatr* 1985; **24**: 531-3.

18 Koletzko B, Majewski F. Congenital anomalies in patients with choanal atresia: CHARGE-association. *Eur J Pediatr* 1984; **142**: 271-5.

19 Leclerc JE, Fearon B. Choanal atresia and associated anomalies. *Int J Pediatr Otorhinolaryngol* 1987; **13**: 265-72.

20 Duncan NO, Miller RH, Catlin FI. Choanal atresia and associated anomalies: the CHARGE association. *Int J Pediatr Otorhinolaryngol* 1988; **15**: 129-35.

21 Cyran SE, Martinez R, Daniels S, St J Dignan P, Kaplan S. Spectrum of congenital heart disease in CHARGE association. *J Pediatr* 1987; **110**: 576-8.

22 August GP, Rosenbaum KN, Friendly D, Hung W. Hypopituitarism and the CHARGE association. *J Pediatr* 1983; **103**: 424-5.

23 Curatolo P, Libutti G, Brinchi V. Infantile spasms and the CHARGE association. *Dev Med Child Neurol* 1983; **25**: 367-73.

24 Ho CK, Kaufman RL, Podos SM. Ocular colobomata, cardiac defect, and other anomalies: a study of seven cases including two sibs. *J Med Genet* 1975; **12**: 289-93.

25 Russell-Eggitt IM, Fielder AR, Levene MI, Young ID. Microphthalmos in a family. *Ophthalmic Paediatr Genet* 1985; **6**: 121-8.

26 Fielder AR, Russell-Eggitt IM, Dodd KL, Mellor DH. Delayed visual maturation. *Trans Ophthalmol Soc UK* 1985; **104**: 653-61.

27 Flynn JT. In: Harley RD, ed. *Pediatric ophthalmology*. 2nd ed. Philadelphia: Saunders, 1983; 1: 13-4.

28 François J. Colobomatous malformations. *Int Ophthalmol Clin* 1968; **8**: 797-876.

29 Mansour AM, Wang F, Henkind P, Goldberg R, Shprintzen R. Ocular findings in the facioauriculovertebral sequence (Goldenhar-Gorlin syndrome). *Am J Ophthalmol* 1985; **100**: 555-9.

30 Collins ET. Case with symmetrical congenital notches in the outer part of each lower lid and defective development of the malar bones. *Trans Ophthalmol Soc UK* 1900; **20**: 190.

- 31 Lessick ML, Szego K, Wong PKW. Trisomy 22 mosaicism with normal blood chromosomes. *Clin Pediatr (Phila)* 1988; 27: 451-4.
- 32 Schinzel A, Schmid W, Fraccaro H, *et al.* The 'cat eye syndrome': dicentric small marker chromosome probably derived from a no. 22 (tetrasomy 22pter -> q11) associated with a characteristic phenotype. *Hum Genet* 1981; 57: 148-58.
- 33 Barakat AY, Butler MG. Renal and urinary tract abnormalities associated with chromosome aberrations. *Int J Pediatr Nephrol* 1987; 8: 215-26.
- 34 Tovo PA, Davi G, Franceschini P, Delpiano A. Thymic hormone dependent immunodeficiency in an infant with partial trisomy of chromosome 22. *Thymus* 1986; 8: 313-8.
- 35 Boles DJ, Bodurtha J, Nance WE. Goldenhar complex in discordant monozygotic twins: a case report and review of the literature. *Am J Med Genet* 1987; 28: 103-9.
- 36 Evans JA, Reggin J, Greenberg C. Tracheal agenesis and associated malformations: a comparison with tracheoesophageal fistula and the VACTERL association. *Am J Med Genet* 1985; 21: 21-34.
- 37 Weaver DD, Mapstone CL, Yu P-I. The VATER association. *Am J Dis Child* 1986; 140: 224-9.
- 38 Taylor A. Autosomal trisomy syndromes. A detailed study of 27 cases of Edwards syndrome and 27 cases of Patau's syndrome. *J Med Genet* 1968; 5: 227.
- 39 Lillquist K, Warburg M, Andersen SR, Hagerstrand I. Coloboma of the iris, ciliary body and choroid in an infant with oesophago-tracheal fistula and congenital heart defects. An unknown malformation complex. *Acta Paediatr Scand* 1980; 69: 427-30.