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Ocular complications in homocystinuria—early and late treated*

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SUMMARY Homocystinuria due to cystathionine-β-synthetase deficiency is an autosomal recessive disorder of methionine metabolism with an incidence in Ireland of 1 in 52 544 births. Ocular complications in untreated patients include ectopia lentis, secondary glaucoma, optic atrophy, and retinal detachment. There are no characteristic signs or symptoms in infancy, and early detection relies on screening of newborn babies. Nineteen patients with homocystinuria were studied; 14 received dietary treatment and vitamin supplementation starting in the newborn period. Of these, none developed ectopia lentis after a mean follow-up of 8·2 years, compared with a 70% dislocation rate in untreated patients with a similar follow-up period. Ectopia lentis developed and progressed in five patients diagnosed later in life, despite tight biochemical control. The risk of ocular complications in homocystinuria can be substantially reduced in patients started on treatment within six weeks of birth.

Homocystinuria due to cystathionine-β-synthetase deficiency is the second most common inborn error of amino acid metabolism. It is an autosomal recessive disorder of methionine metabolism first described in 1962.[1,2] Plasma homocysteine is increased, chiefly as the disulphide homocystine (homocysteine-homocysteine), and spills into the urine.[3] Plasma methionine is likewise increased and plasma cysteine and cystine are decreased. Two disorders of cystathionine-β-synthetase exist; both produce the same amino acid abnormalities and clinical features. One form responds to pharmacological doses of pyridoxine (vitamin B_6), the other more common and more severe form is pyridoxine-unresponsive and requires a low-methionine diet supplemented with cystine.

The incidence of homocystinuria in Ireland is 1 in 52 544 newborns screened (Cahalane S, personal communication). Not all countries or regions within countries screen for this disorder because of its variable, geographical incidence, which is as rare as 1 in 573 000 newborns in some European countries.[4]

Untreated patients have ectopia-lentis, mental retardation, skeletal disorders and thromboembolic episodes[3] which can lead to death by 20 years of age. The major ocular complication is ectopia lentis, which probably occurs in up to 70% of patients by 8 years of age and in more than 95% by 40 years.[5] We describe the ocular findings in 19 patients with homocystinuria due to cystathionine-β-synthetase deficiency and correlate these findings with the age at commencement of treatment and biochemical control.

Patients and methods

Nineteen patients with homocystinuria were studied. There were 10 males and nine females, aged 4·4 to 17·3 years. Fourteen patients were detected by screening (group 1; Table 1) and were on treatment from the first six weeks of life, while five patients began treatment in childhood (group 2; Table 2). The Guthrie microbiological inhibition assay for methionine was used for screening, performed on a dried blood spot between the third and sixth days of

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life. The diagnosis was confirmed by the demonstration of increased plasma homocyst(e)ine (homocystine plus homocysteine) and methionine and decreased plasma cyst(e)ine (cystine plus cysteine).[3] Cystathionine-β-synthetase activity was assayed in cultured skin fibroblasts of seven randomly chosen patients (Tables 1 and 2). The pyridoxine status of all patients was determined.

All patients attend the Inherited Metabolic Unit. One patient (case 17) responded to pyridoxine and folate supplements. The remainder required a low-methionine diet supplemented with cystine. The diet was monitored and adjusted in accordance with monthly or bimonthly measurement of plasma methionine, homocyst(e)ine, and cyst(e)ine.[6] Pyridoxine supplementation was reinstituted in all pyridoxine-unresponsive patients (14 of 17 cases) on the theoretical assumption that some residual enzyme activity might be stimulated, enabling more methionine to be tolerated. Biochemical control was defined as good if homocyst(e)ine levels were <10 μm/l, fair 10–15 μm/l, and poor if >15 μm/l. We also classified control for cyst(e)ine as good if >22 μm/l, fair 12–21 μm/l, and poor <12 μm/l.

Each patient underwent a detailed ophthalmic examination which included testing of visual acuity, motility assessment, cycloplegic retinoscopy, slit-lamp biomicroscopy, and direct and indirect ophthalmoscopy. Historical information was obtained from the medical records. We correlated ophthalmic findings in each patient with biochemical control as reflected by mean plasma homocyst(e)ine[7] and cyst(e)ine[8] levels since the beginning of therapy.

Results

Fourteen patients (seven males and seven females) were detected on newborn screening (group 1, Table 1). Their mean age at the start of treatment was 22·7 days, range 7 to 42 days. The mean period of follow-up was 8·2 years, range 3·9 to 15·3 years. Cases 10 and 11 were partially pyridoxine-responsive and the remaining 12 cases were pyridoxine-unresponsive. All patients required a low-methionine diet supplemented with cysteine.

Four patients were poorly controlled with respect to mean plasma homocyst(e)ine (cases 9, 12, 13, and 14) while case 9 was well controlled with respect to mean plasma cyst(e)ine. All patients had corrected visual acuities of better or equal to 20/30. None of the patients in group 1 have developed ectopia lentis. Cases 12 and 13, aged 15·3 and 8·1 years, who were poorly controlled with respect to homocyst(e)ine, have become increasingly myopic. Four patients have marked benign peripheral cystoid degeneration (cases 10, 11, 12, and 13). Case 14, aged 3·9 years, had an episode of bilateral optic disc oedema and ataxia during a period of poor dietary compliance; spontaneous resolution followed normalisation of biochemical control.

SELECTED CASES

Case 13 began treatment at 42 days and was poorly controlled because of poor compliance. At the most recent assessment this child was myopic (OD −6·5 sphere, +1·0 cylinder, axis 5°; OS −5·5 sphere, +1·0 cylinder, axis 170°), but one year previously refrac-

Table 1 *Summary of age data, major eye findings, and biochemical control for patients in group 1 (newborn screening)*

Case no.	*Sex*	*Age therapy commenced (days)*	*Age now (years)*	*Mean biochemical control**		*Ocular abnormalities*
				Plasma homocyst(e)ine	*Plasma cyst(e)ine)*	
1†	F	35	14·2	Good	Good	–
2	M	22	4·4	Fair	Fair	Hypermetropia
3	M	21	6·3	Good	Good	–
4	M	13	5·5	Good	Good	Hypermetropia
5	F	15	6·3	Fair	Fair	Hypermetropia
6†	F	28	4·4	Good	Fair	Hypermetropia
7	F	8	8·8	Fair	Good	–
8	M	7	5·0	Good	Good	Hypermetropia
9†	F	26	7·5	Poor	Good	Hypermetropia
10‡	M	10	12·6	Good	Good	PCRD
11‡	M	36	13·5	Good	Good	PCRD
12†	M	42	15·3	Poor	Fair	Myopia, PCRD
13	F	42	8·1	Poor	Poor	Myopia, PCRD
14	F	13	3·9	Poor	Fair	Hypermetropia, optic disc oedema

*Mean biochemical control, for homocyst(e)ine (good <10 μmol/l; fair 10 to 15 μmol/l; poor <15 μmol/l), for cyst(e)ine (good >22 μmol/l; fair 12 to 21 μmol/l; poor <12 μmol/l).

PCRD=Peripheral cystoid retinal degeneration.

†Cystathionine-β- synthetase activity assessed—negligible or undetectable.

‡Partially pyridoxine responsive.

tion was OD +1·0; OS +1·0. The corrected visual acuity was 20/20 in each eye and there was no evidence of ectopia lentis. She had peripheral cystoid retinal degeneration extending circumferentially through 360° posterior to the globe equator.

Case 12 began treatment at 42 days and was poorly controlled since diagnosis. His corrected visual acuity was 20/30 in each eye and became increasingly myopic with time (1978: OD +0·75 sphere, +1·75 cylinder, axis 115°; OS +1·0 sphere, +2·0 cylinder, axis 60°; 1983: OD −2·0 sphere, +3·0 cylinder, axis 120°; OS −2·75 sphere, +2·25 cylinder, axis 30°; 1987: OD −8·0 sphere, +3·25 cylinder, axis 120°; OS −5·0 sphere, +3·25 cylinder, axis 50°). The lens examination was unremarkable and funduscopy showed peripheral cystoid retinal degeneration extending circumferentially through 360° posterior to the equator.

Five patients (three males and two females) were detected later in life (group 2, Table 2). Their mean age and commencement of treatment was 3·7 years with a range of 1·5 to 7 years. The mean period of follow-up was 9 years, range 4·8 to 15·8 years. Case 17 was pyridoxine-responsive, while the remainder were pyridoxine-unresponsive. Cases 15, 16, and 17 initially presented to the ophthalmologist with poor vision due to bilateral ectopia lentis. Case 19 presented at 1·5 years with an intracranial haemorrhage and seizures. Case 18 was diagnosed at 2·4 years after identification of homocystinuria in a sibling on neonatal screening. Ectopia lentis progressed or developed in all patients in group 2 despite good biochemical control. The corrected visual acuity was better than or equal to 20/30 in three eyes, 20/40 in four eyes, and 20/120 in one eye with strabismus. Visual acuity was indeterminable in case 19 owing to mental retardation.

Case 15 presented with bilateral symmetrical inferonasal ectopia lentis at 2·9 years. Despite tight biochemical control both lenses continued to dislocate downwards, and this was associated with increasing myopia (1985: OD −5·5 sphere, OS −3·50 sphere; 1987: OD −8·50 sphere, OS −5·5 sphere).

Case 16 presented at 4·8 years with bilateral symmetrical inferonasal ectopia lentis and high myopia. There has been progressive lens dislocation in both eyes despite tight biochemical control to the extent that the patient required aphakic correction of +14·50 dioptre spheres in each eye.

Case 17 was pyridoxine-responsive and presented with bilateral symmetrical superonasal ectopia lentis and compound myopic astigmatism at 7 years. Since then both lenses continued to dislocate, with an associated increase in myopic astigmatism despite tight biochemical control.

Case 18 showed normal appearances on eye examination when treatment began at 2·4 years of age. One year later a unilateral left inferonasal lens dislocation was present in the absence of trauma. So far the right lens has appeared normal. The corrected visual acuity was 20/20 in each eye, and there was bilateral peripheral cystoid retinal degeneration.

Case 19 presented with an intracranial haemorrhage, spherophakia, and simple myopia at 1·5 years. Within six months he was noted to have early bilateral superonasal ectopia lentis, which continued to progress slowly despite tight biochemical control. His latest refraction was OD −11·50 sphere, +3·50 cylinder, axis 90°; OS −11·0 sphere, +2·0 cylinder, axis 95°. In 1980 the refraction was OD −5·0 sphere, +3·0 cylinder, axis 85°; OS −5·50 sphere, +3·50 cylinder, axis 90°. Funduscopy showed marked peripheral cystoid retinal degeneration extending to the globe equator.

Discussion

Ectopia lentis is the ocular hallmark of homocystinuria due to cystathionine-β-synthetase deficiency[9] and may be preceded for several years by myopia.[10] The mechanism by which the observed biochemical abnormalities produce the clinical

Table 2 *Summary of age data, medical and major eye findings, and biochemical control for patients in group 2 (late detected)*

Case no.	*Sex*	*Age therapy commenced (years)*	*Age now (years)*	*Medical and ophthalmic findings at diagnosis*	*Mean biochemical control*		*Ocular findings now*
					Homocyst(e)ine	*Cyst(e)ine*	
15	F	2·9	8·7	Mental retardation myopia, ectopia lentis	Good	Good	Myopia, ectopia lentis
16	F	4·8	15·8	Myopia, ectopia lentis	Good	Good	Ectopia lentis, aphakic glasses
17‡	M	7·0	13·3	Myopia, ectopia lentis	Good	Good	Myopia, ectopia lentis
18	M	2·4	8·5	Mental retardation hypermetropia	Good	Good	L ectopia lentis, L anisometropia, PCRD
19†	M	1·5	17·3	Cerebrovascular accident myopia spheroplakia	Good	Good	Myopia, ectopia lentis, PCRD

†Cystathionine-β-synthetase activity assessed—negligible or undetectable.
‡Pyridoxine responsive.

features of this disorder has not been fully explained, but there is evidence to suggest that it is related to the abnormal levels of homocyst(e)ine[7] and cyst(e)ine.[8] Lens zonules normally have a high cysteine content, and its deficiency may affect normal zonular development, thereby predisposing to myopia and lens dislocation. Homocysteine inhibits cross-linkage in collagen and elastic tissue and predisposes to zonule degeneration. The lens dislocation is invariably bilateral and is frequently inferior, but the position is not diagnostic, as the lens may migrate in any direction.[11] In our five patients with lens dislocation the lens in three migrated inferonasally and in two superonasally.

The diagnosis of homocystinuria may be difficult, as the age of onset, severity, and pattern of clinical manifestations vary widely among affected patients.[12] Likewise homocystine levels vary widely, and tests based on methionine loading may confirm the diagnosis in suspected cases missed on routine screening.[13] The typical untreated homocystinuric is asymptomatic in infancy and subsequently develops ectopia lentis, mental retardation, skeletal disorders, and thromboembolic episodes which may be fatal. The prevalence and natural history of these complications remain uncertain owing to the short interval between original discovery and initiation of various therapies. Present limited evidence indicates that the advent of effective neonatal screening programmes, combined with the introduction of effective diet and pharmacological therapy in the neonatal period, has improved the prognosis. However, the ophthalmic benefit of treatment initiated in the newborn period remains uncertain because of the small numbers of patients studied so far.

None of our 14 patients detected on routine screening and started on dietary treatment within six weeks of birth have developed ectopia lentis over a mean follow-up of 8·2 years. Mudd *et al.*[5] suggest that the probability of ectopia lentis developing in untreated pyridoxine-unresponsive patients by 8·2 years is in excess of 70%. However, two poorly controlled patients within this group (cases 12 and 13) have recently developed myopia. This may be the harbinger of ectopia lentis in this subgroup, and longer follow-up is required.

The outcome in late detected cases whose treatment is initiated prior to the development of ectopia lentis is not clear, but two such cases (18 and 19) in our series developed ectopia lentis despite tight biochemical control within 1·5 and 0·5 years of initiation of therapy. Boers[14] followed up five such pyridoxine-responsive cases for periods ranging from 0·5 to 13 years and none developed ectopia lentis. Grobe[15] suggests that ectopia lentis occurs in such cases but to a milder degree. Mudd *et al.*[5] state that therapy may reduce the lens dislocation rate in pyridoxine-responsive cases but may not confer statistically significant benefit on lens dislocation in pyridoxine-unresponsive patients. It is clear from our present data that ectopia lentis progresses despite tight biochemical control in late detected cases.

Ectopia lentis is bilateral in the vast majority of patients with homocystinuria. Case 18 in our series developed unilateral ectopia lentis within 18 months of beginning a diet and has been followed up for four years with no change in the position of the contralateral lens to date.

Benign peripheral cystoid retinal degeneration extending circumferentially to the globe equator occurred in six of our 19 patients. No case progressed to degenerative retinoschisis. Ramsay and colleagues[16] suggest on the basis of histological studies that, in addition to ectopia lentis, peripheral cystoid retinal degeneration may also be observed as a characteristic clinical finding in some cases of homocystinuria. They also suggest that the pathogenesis of cystoid degeneration and that of ectopia lentis may be interrelated because of their common embryological origin. They note that the severity of the changes are age related and depend on patient survival. Peripheral cystoid retinal degeneration is the most common peripheral degeneration[17] present to some degree in all eyes after 8 years of age and gradually increases with age. In contrast to ectopia lentis and myopia we found no relationship between the age at start of treatment, adequacy of biochemical control, and peripheral cystoid retinal degeneration; but the number of patients are small and the follow-up period is relatively short. It is possible that patients with homocystinuria on an altered amino acid intake may be more susceptible to an acceleration of an otherwise common degenerative process.

Ocular complications are common in patients with homocystinuria. Ectopia lentis is the most significant in that it occurs in almost all cases, impairs visual acuity, and precipitates secondary sight threatening complications, including secondary glaucoma and retinal detachment. Lens extraction is probably associated with a greater incidence of ocular complications such as retinal detachment, and with intra- and postoperative mortality due to thromboembolic episodes. Newborn screening followed by tight biochemical control prevented ectopia lentis in 11 of 14 patients (mean follow-up 8·2 years). Myopia without ectopia lentis occurred in two of 14 patients with less tight biochemical control. In contrast, ectopia lentis developed and progressed in five late-detected patients despite tight biochemical control. These results suggest that early treatment may significantly and beneficially alter the natural ophthalmic course

of homocystinuric patients. The relationship between peripheral retinal changes and homocystinuria requires further evaluation.

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