CLINICAL STUDY

Ophthalmic abnormalities in homocystinuria: the value of screening

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Abstract

Purpose **Homocystinuria, a genetic metabolic abnormality, eventually causes a variety of ocular and other pathologies if not treated. To evaluate the results of screening newborns for homocystinuria, we compared ophthalmic outcomes for two groups of homocystinuria patients who had been diagnosed either at birth or later than 6 weeks.**

Methods and results **Nineteen patients had been screened and diagnosed shortly after birth, with treatment instigated before 6 weeks of age (mean follow-up and age 10.8 years; median 11 years). Eight of 17 were myopic; 13 of 15 had good vision in both eyes; one had lens subluxation. The second group of 17 patients were diagnosed later than 6 weeks, often (12 patients) because of ocular problems (mean follow-up 8.3 years; mean age 19.4 years; median age 16 years). Visual function varied from 6/6 (4 patients) to less than 6/36 (4 patients); 3 eyes had no perception of light. Thirteen patients had lens subluxation or dislocation.**

Conclusion **Early diagnosis and treatment of homocystinuria is advantageous.**

Key words Ectopia lentis, Homocystinuria, Myopia, Screening

Homocystinuria due to cystathionine β-synthase (CBS) deficiency is the commonest disorder of amino acid metabolism. CBS deficiency is an autosomal recessive disorder. The protein is coded on chromosome 21 (21q22.3).[1] Considerable genetic heterogeneity exists, and at least 13 different mutations of the CBS protein have been identified.[1–6] Some work has been published on phenotypic correlations with specific DNA/protein mutations.[2–6] Phenotypic variability between siblings with the same genotype has also been described.[4,5]

In Ireland[7] the prevalence of homocystinuria is 1 in 52 544 births, in the United Kingdom (Manchester)[8] 1 in 96 000; and in the United States[8] it is 1 in 406 000. The prevalence of homocystinuria in the USA has been linked to patients with Celtic ancestry.[3]

CBS deficiency affects the excretion of sulphur, with accumulation of homocyst(e)ine and methionine and depletion of cysteine. Homocyst(e)ine is the sum of homocysteine, homocystine and homocysteine–cysteine disulphide in free and protein-bound forms. These metabolic abnormalities cause a wide range of ocular, cerebral, skeletal and clotting pathologies. Ocular sequelae characteristically involve visual loss associated with subluxation of the crystalline lens and myopia, although glaucoma, optic atrophy, retinal degeneration, retinal detachment, cataracts, corneal abnormalities, and atrophy of non-pigmented ciliary epithelium also occur.

The biochemical abnormality can be corrected in some patients by oral pyridoxine – so-called pyridoxine-responsive disease. Pyridoxine stimulates any residual activity of CBS. If this is unsuccessful dietary restriction of methionine and supplementation of cysteine may be required (pyridoxine non-responsive). Oral betaine may be administered as a methyl donor to facilitate the conversion of homocysteine back to methionine. With dietary compliance, the biochemical irregularities are corrected.

Since this condition exists in a pre-symptomatic form, widespread screening for homocystinuria, especially in high-risk areas, would be advantageous to patients if early treatment can be shown to be beneficial. To evaluate the results of screening newborns, we compared ophthalmic outcomes for homocystinuria patients who were diagnosed very early with the outcomes of those who were diagnosed late.

Patients and methods

In some regions in Ireland newborns are being screened using the Guthrie microbiological inhibition assay for methionine. This is carried out on a dried blood spot between the 3rd and the 6th day of life. The diagnosis is confirmed by the demonstration of increased plasma homocyst(e)ine and methionine and decreased plasma cysteine. The pyridoxine status was determined *in vitro*, but a trial of oral pyridoxine

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was administered in all patients. Eighteen consecutive patients from this programme who were found to have homocystinuria have been followed prospectively over the last 20 years. Their ophthalmic status is presented (group A). Group A also includes patient 19, who was not from this programme but was diagnosed at 4 weeks of age as a result of severe systemic illness.

Group B patients were diagnosed as a result of investigations of various clinical manifestations; treatment was commenced following diagnosis. Of the 17 patients included in this group, seven were from Ireland and ten were from the United Kingdom. These UK patients were on record at the Sheffield Children's Hospital as having homocystinuria (an eleventh patient was excluded whose homocystinuria resulted from disordered B_{12} metabolism). Ten of the 17 patients were recalled and examined, and in seven cases information was obtained from their own ophthalmologist. Information obtained included assessment of corrected visual acuity, refraction (cycloplegic where appropriate), and examination findings from slit lamp biomicroscopy and ophthalmoscopy (direct and indirect). Data on refraction were averaged from the two mean spherical equivalents for each patient.

In all patients an assessment was made as to dietary compliance. This was categorised as good, fair or poor. All available assays of plasma homocyst(e)ine and cysteine were obtained and the mean value and standard deviation calculated.

Results

The ophthalmic assessments of the two groups are presented in Table 1 (group A) and Table 2 (group B, with additional information on the mode of and age at presentation).

Group A patients had a mean age of 10.8 years, a median age of 11 years, and a range of 1–20 years. Nine were pyridoxine-responsive and a further five showed some biochemical improvement with pyridoxine. Ten patients had 6/6 vision in each eye; four had good central fixation, with no quantitative visual acuity yet established. Eight of 17 patients (data were unavailable for two patients) were myopic. One patient had subluxed lenses. Patient 4 had optic disc oedema, which was transient and temporally associated with a period of poor biochemical control.

The mean age of group B patients was 19.4 years (median 16 years, range 5–63 years); the mean age at diagnosis was 11 years (median 7 years, range 1–47 years). These calculations excluded patient 19 from group A. The mean length of follow-up was 8.3 years (range 1–16 years). Five patients were pyridoxine-responsive; three showed some biochemical improvement with pyridoxine. In five children, increasing myopia was an early abnormality. In five patients the diagnosis was made following dislocation of the lens, associated with an acute rise in intraocular pressure. Lens dislocation occurred in patient 11 at the age of 33 years; the diagnosis was established at the time

Table 1. *Data on 19 homocystinuria patients diagnosed within 6 weeks of birth (group A)*

Patient no.[a]	Follow-up (yr)	Pyrx[b]	Dietary compliance	Visual acuity[c]		Refraction[d]	Ocular exam.[e]	Plasma homocyst(e)ine (μmol/l)[f]		Plasma cysteine (μmol/l)	
				OD	OS			Mean	Range	Mean	Range
1*	12	Yes	Good	6/6	6/6	+2	Normal	10.5	7–14	31	11–54
2	13	Yes	Good	6/9	6/9	−5.5	Normal	22.0	0–52	28.8	15–75
3†	5.0	Yes	Good	6/6	6/6	+2	Normal	12.0	0–22	25	17–39
4†	10	No	Poor	6/6	6/6	−0.37	Disc oedema	50.0		25	7–42
5	10	Part	Good	6/12	6/9	+0.62	Normal	10.3	0–13	33	23–41
6†	19	No	Poor	6/9	6/9	−5.75	Normal	19.0		14	
7	19	No	Fair	6/6	6/6	−0.75	Blue dot	13.0	8–25	35	13–46
8	11	Yes	Good	6/6	6/6	+0.5	Blue dot	13.2	7–40	32.6	12–63
9	10	No	Good	6/6	6/6	+0.5	Normal	7.9	0–28	29.5	0–47
10‡	11	Yes	Good	6/6	6/6	−0.5	Normal	5.6	0–17	29	11–40
11	13	Part	Fair	6/6	6/6	+1.62	Normal	58.4	24–73	11.9	6–17
12	14	Part	Poor	6/24	6/24	−12.3	Sblx down, hypo. fundus	13.7	0–24	28.4	10–43
13	16	Part	Fair	6/6	6/6	−0.5	Normal	19.6	0–55	30.6	19–46
14	20	Part	Fair	6/6	6/6		Pup. m., pig. deg.	20.5	0–45	29	10–42
15	3.0	Yes	Good	CSM	CSM	+2.5	Normal	5	0–13	23.4	14–33
16	1.4	Yes	Good	CSM	CSM	+5	Normal	11	0–21	22.5	11–33
17	1.5	Yes	Good	CSM	CSM	+5	Normal	9.5	5–17	24.5	21–29
18	4.0	Yes	Good	CSM	CSM		Normal	13.2	9–14	21.2	21–26
19†	13	No	Poor	6/18	6/6	−1.31	Normal	13.0	0–77	26.1	6–52

Blank spaces represent missing data.
[a]Other diagnoses: * speech delayed; † recurrent upper respiratory illnesses; ‡ bony changes.
[b]Pyridoxine responsiveness. Part, partially responsive to pyridoxine.
[c]OD, right eye; OS, left eye; CSM, central fixation steady and maintained.
[d]Mean of two mean spheres.
[e]Abnormal ocular examination findings. Disc oedema, optic disc oedema; sblx down, lens subluxing down; hypo. fundus, hypopigmented fundus; Pup. m., pupillary membrane; pig. deg., peripheral retinal pigmentation.
[f]Treated values should be less than 10.

Table 2. *Data on 17 homocystinuria patients diagnosed at ⩾ 6 weeks of age (group B)*

Patient no.[a]	Age at diagnosis (years)	Why diagnosed[b]	Follow-up (yr)	Pyrx[c]	Dietary compliance	Visual acuity[d] OD	Visual acuity[d] OS	Refraction[e]	Lens[f]	Ocular exam.[g]	Plasma homocyst(e)ine (μmol/l)[h] Mean	Plasma homocyst(e)ine (μmol/l)[h] Range	Plasma cysteine (μmol/l) Mean	Plasma cysteine (μmol/l) Range
1	3		11	Yes	Good	6/6	6/6	Plano	Sblx up	Nil else	7.0	0–20	28.5	15–52
2	7	Myopia	10	Part	Fair	6/12	6/9	−7.75	Sblx up	ET	8.5	0–12	27.6	17–48
3	3	Myopia	12	Part	Poor	6/12	6/18	−11	Sblx down	Nil else	31.8	19–40	7.8	0–14
4*†	1.3	Seizures	15	No	Good	6/6	6/6	−9.125	Sblx up	Psclo	3.4	0–14	28.5	19–38
5	4	Dislocatn	11	No	Good	6/12	6/12	+14	Dislocatn	Nil else	21.5	0–65	28.4	3–35
6*†	25	Dislocatn	1.0	Part	Poor	6/18	6/60	+10.5	Dislocatn	PKP	61		28	
7‡	11	Dislocatn	15	No					Aphakic Dislocatn	RD	13		27	
8‡	6	Myopia	13	Yes		6/60	6/60	−22.62	Sblx down	XT	7.1		36.2	
9	14	Sib	11	No	Fair	6/36	NPL			RD	34.9	0–119	19.8	0–58
10	11	Dislocatn	10	No	Poor	NPL	6/18	+6.75	Dislocatn	Prosthetic	52.2	0–106	14.1	0–52
11§	47	Dislocatn	16	Yes	Poor	NPL	6/60		Aphakic Dislocatn	RD	0.16	0–3	48.6	5–73
12†	22	CVA	3	Yes		6/6	6/6		Norm	Nil else	5.27	0–32	56.9	21–88
13	2	Sib	3	No	Fair	6/6	6/6				11.3	0–62		
14	5	Sblx	2	No	Good	6/18	6/18		Sblx	Nil else	7.1	0–56		
15	6	Myopia	4	Yes	Good	6/12	6/12	−14	Sblx up	Nil else	26.4	0–77		
16¶	9	Myopia	2	No		6/60	6/60	−10.5	Dislocatn	Nil else	58	10–77		
17¶	12	Dislocatn	2	No					Aphakic Dislocatn	Nil else	5		33	

Blank spaces represent missing data.
[a]Other diagnoses: * developmentally delayed; † thrombotic event (patient 4, cerebrovascular accident; patient 6, cerebrovascular accident resulting in death; patient 12, cerebral thrombosis and subsequent deep vein thrombosis; ‡ recurrent upper respiratory illnesses; § ischaemic heart disease; ¶ bony changes.
[b]Reason for diagnosis: dislocatn, lens dislocation; CVA, cerebrovascular accident; sblx, lens subluxing.
[c]Pyridoxine responsiveness. Part, partially responsive to pyridoxine.
[d]OD, right eye; OS, left eye; NPL, no perception of light.
[e]Mean of two mean spheres. Plano, no refraction required.
[f]Sblx, subluxation (patient 14 subluxation direction unknown); Dislocatn, dislocation.
[g]Abnormal ocular examination findings other than lens finding. ET, esotropia; psclo, posterior subcapsular lens opacity; PKP, penetrating keratoplasty; RD, retinal detachment; XT, exotropia; prosthetic, prosthetic eye.
[h]Treated values should be less than 10.

of retinal detachment surgery, 14 years later. Only four patients had 6/6 vision in each eye, and four patients had vision of 6/36 or worse in their better eye. Seven of eight patients who had not had lens removal were myopic. Three patients have undergone surgery for retinal detachment in one or both eyes; one further patient required enucleation following endophthalmitis complicating lens extraction.

Discussion

There are interesting observations to be made about each group of patients independently as well as when comparing the two groups. Group B cannot be designated a control group, as all these patients presented with significant disease. Although the follow-up time is comparable, group B patients are older on average (19.4 vs 10.8 years). However, the median ages are far more comparable (16 vs 11 years), as the age distribution of group B was skewed to a younger age.

The visual function of group A patients was generally better than that of group B patients. In group B, three eyes from three patients were blind (no perception of light): two from retinal detachment and one following endophthalmitis.

In group A, 8 (47%) of 17 were myopic – a prevalence higher than that commonly reported for the general population (10–25%). Increased prevalence of myopia in homocystinuria has been previously described[9] and has been thought to be from increased curvature of the lens because of poor zonular tension. An anterior shift of the lens may also induce similar refractive changes. The zonules are composed of a glycoprotein with a high concentration of cysteine[10] – which may explain their susceptibility in this condition, in which cysteine is depleted. Axial lengths were not measured in these patients; normal axial length measurements with normal keratometry readings would strongly suggest that the myopia is due to increased curvature or anterior movement of the lens.

In group B, myopia was even more common (7 of 10 known refractions), and when present was higher in value than in group A. Increasing myopia in early childhood was a feature in five of the patients prior to diagnosis.

Zonular weakness also leads to lens subluxation and dislocation. No patient in group A had lens dislocation, and only one had lens subluxation – patient 12, currently 14 years old. This patient was extremely myopic, with a refraction of −13.5/+1.25 × 4 right eye and −12.75/

+1.75 × 70 left eye. Her documented biochemical control was fair; her dietary compliance was poor. The prevalence of lens dislocations has been previously reported[10] as 50% in untreated pyridoxine non-responders by age 6 years and 50% in untreated pyridoxine responders by age 10 years.

A previous report[11] explored the effect of early diagnosis and treatment on various aspects of homocystinuria. Methionine restriction prevented mental retardation, reduced the rate of lens dislocation, and may have reduced the incidence of seizures. Our data support the impression that early treatment at least delays the onset of ectopia lentis.

In group B seven patients had dislocation and a further seven had evidence of marked zonular damage. The general health of group B patients was worse, with two patients suffering life-threatening cerebral vascular accidents and one patient having died.

In patient 11, group B, a dislocated lens failed to alert the ophthalmologist to the diagnosis. This was probably due to the age of the patient at the time (33 years). Although this must be an unusual case, it serves to illustrate that ophthalmologists treating adults may encounter new presentations of this condition, which is usually diagnosed in children.

The age of diagnosis of non-screened patients varied widely – from 4 weeks to 47 years. The median age was 7 years. It is interesting that ocular problems were prominent in the diagnostic process in 12 of the 17 group B patients.

Group B patients required many surgical procedures. This is of particular concern, as the metabolic abnormality is associated with an increased risk of anaesthetic complications. There have been no surgical procedures carried out on group A patients to date. Six patients from group B required lens extraction, five of whom presented with acute glaucoma. Three patients subsequently required retinal detachment repairs; vitreoretinal procedures were required in patient 11. Patient 10 suffered a series of complications following cataract surgery, namely wound rupture, wound repair, endophthalmitis and subsequent enucleation.

Should screening for homocystinuria be recommended in the UK? Screening newborns for homocystinuria is routinely carried out in 21 states in the USA.[12] Homocystinuria is not a condition characterised by illness in the neonatal period. Raised plasma methionine may not be present until the 2nd or 3rd day; with the trend to early discharge post-partum, this may represent a logistic problem. Homocystinuria is characterised by a varied clinical presentation and an onset at a variety of ages. Genetic evaluation is teaching us that phenotypic variability can occur even with the same genetic mutation.

Biochemically screened patients treated at an early age have better vision, less myopia and lens subluxation, require fewer surgical procedures and are generally healthier than a group of non-screened patients diagnosed later in life.

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