

# Homocystinuria

## Review of four cases

M. RAHMAN

*North Middlesex Hospital, London*

Homocystinuria is an inborn error of methionine metabolism. Since it was first described by Carson and Neill (1962) in two patients in Northern Ireland, more than 100 cases have been described in the literature.

The site of biochemical abnormality was explained by Mudd, Finkelstein, Irreverre, and Laster (1964), who suggested that there was a deficiency or absence of the enzyme cystathionine synthetase which is responsible for converting the essential sulphur-containing amino acid methionine into cystine and its end-products. This results in increased concentration of methionine and homocystine in the blood and cerebrospinal fluid, and an increased excretion of homocystine in the urine. Clinically, there is a characteristic picture of mental retardation, ectopia lentis, fair complexion, fair hair, high cheek colour, thrombo-embolic episodes, and skeletal changes (Carson, Cusworth, Dent, Field, Neill, and Westall, 1963; Carey, Donovan, FitzGerald, and McAuley, 1968; Presley, Stinson, and Sidbury, 1968, 1969). General pathological findings have been described in detail in a few cases (Carson, Dent, Field, and Gaull, 1965; Carey and others, 1968; McCully 1969), and Henkind and Ashton (1965) first described the histological picture in four eyes. No satisfactory treatment is at present available for the condition, but the ocular treatment is, by choice, conservative.

During the last 2½ years, four cases have been seen in routine out-patient practice (Table).

**Table** *Salient features of four cases*

Feature	Case no.			
	1	2	3	4
Ectopia lentis	+	+	+	+
Mental retardation	+	+	+	+
Fair complexion	+	+	+	+
Fair hair	+	+	+	+
High cheek colour	+	+	+	+
Skeletal changes	None	Genu valgum High arched palate	High arched palate	Generalized osteoporosis
Spastic gait	+	—	—	+
“Marfan’s syndrome”	—	—	—	—
“Marchesani’s syndrome”	—	+	—	—
Parental consanguinity	—	—	—	—

The diagnosis was confirmed biologically in the following way:

A cyanide-nitroprusside test was performed on the urine. A positive reaction indicated the presence of sulphur-containing amino acids, namely homocystine and/or cystine. These were then differentiated by paper chromatography or supervoltage electrophoresis.

Although these cases were typical enough to be suspected clinically, several unusual features were present.

### Case reports

**Case 1, a 25-year-old man**, was admitted to the ophthalmic ward of Sutton General Hospital on March 3, 1968, with a dislocated lens and secondary glaucoma in the left eye. Symptoms of a painful red eye had persisted for 24 hours before he was brought to the casualty department of the hospital. There was no history of injury.

He was born at term after an uncomplicated pregnancy, the birth weight being 7 lb 2 oz. The milestones of early childhood were delayed. Mental retardation was first noted at the age of 3 years. He had been an in-patient in a psychiatric hospital since the age of 12 years for schizophrenia, and was having occasional violent attacks.

#### Examination

The left eye was injected and the lens was dislocated into the anterior chamber giving rise to secondary glaucoma. The right eye was white, but on dilatation of the pupil the lens in this eye was found to be subluxated downwards and temporally.

He was a co-operative, mild, and easy-going patient. He had features of homocystinuria (Table) namely fair complexion, fair hair, malar flush, and high-stepping spastic gait. Examination of other systems gave negative results.

#### Treatment

After initial hypotensive therapy with acetazolamide, the lens in the left eye was removed by *ab externo* incision and complete sector iridectomy. When the incision was completed, the lens fell back into the posterior chamber and disappeared from sight behind the iris. A gentle saline irrigation brought the lens back into the anterior chamber. It was then removed by using a vectis. There was no loss of vitreous. Recovery was uneventful.

#### Subsequent history

On December 31, 1968, he was re-admitted for anterior dislocation of the lens in the other (right) eye with secondary glaucoma. Management was similar to that for the left eye. The lens was extracted intracapsularly with slight vitreous loss. The postoperative period was uneventful.

Apart from occasional violent schizophrenic attacks, he is otherwise fit and well. The visual acuity is 6/9 in the right eye and 6/6 in the left with aphakic corrections. The ocular tensions and fundi are normal.

**Case 2, a boy aged 4 years**, was first referred to the eye out-patient department of Sutton General Hospital, because his mother thought he had a squint. He had been born at the 42nd week after a normal pregnancy, and was delivered by forceps, the birth weight being 7 lb 3 oz. He needed oxygen for resuscitation, but the neonatal period was otherwise normal. The milestones of early childhood were delayed. He was 18 months old when the parents first noted his slow development.

#### Examination

No squint was detected, but there was bilateral nasal subluxation of the lenses. Refraction was  $-5.5$  D sph. in the right eye and  $-8.5$  D sph.,  $+2.5$  D cyl., axis  $100^\circ$  in the left. The fundi were normal and the ocular tension  $15.9$  mm.Hg (Schiotz) in each eye.

He was of short pyknotic build with strong musculature. His neck was short and his hands short and clumsy. His joints were tight. These features, along with spherophakia prompted the diagnosis of the Marchesani syndrome.

#### *Progress*

At the age of 6 years it was noted that he had some of the typical features of homocystinuria (Table). He was obviously mentally retarded with an estimated I.Q. of 46. There was no abnormality in the cardiovascular system. An abnormal electroencephalogram with paroxysmal notched irregular theta waves in all leads, with a slight similar abnormality during photic stimulation was recorded. There was also an excess of beta activity. There was an erythematous rash on his buttocks. Investigations of other systems revealed no abnormality.

#### *Treatment and result*

##### OCULAR

No treatment was needed apart from the prescription of glasses which were changed from time to time. When last seen, he was thought to be using the aphakic part of his pupils. An aphakic correction was prescribed as follows:

*Right* +12.5 D sph., + 0.75 D cyl., axis 90°,

*Left*: + 12.5 D sph., +1 D cyl., axis 90°.

The visual acuity was recorded as 3/60 in the right eye and 5/60 in the left.

##### GENERAL (carried out at Queen Mary's Hospital, Carshalton)

After the diagnosis of homocystinuria was confirmed, he was started on pyridoxine 500 mg. daily. After a week on pyridoxine, he was started on L-cystine supplements. Biochemically he became much more normal, but there was no obvious change in his mental state. He was discharged home on pyridoxine 500 mg. daily, and on this treatment he has maintained the biochemical improvement.

**Case 3, the younger sister of Case 2**, was referred to the eye out-patient department of Sutton General Hospital in May, 1968, at the age of 4½ years because her mother thought she was "short-sighted" as she frequently fell over. She was born after a normal pregnancy at the 42 week, the birth weight being 6 lb 13 oz. The neonatal period was normal.

#### *Examination*

There was bilateral nasal subluxation of the lenses. She was highly myopic. Refraction was -12 D sph., with visual acuity 6/24 in each eye (Sheridan Gardiner test). The ocular tensions and fundi were normal.

She showed features of homocystinuria (Table). A psychological assessment showed that, though brighter than her brother, she was mentally subnormal. Her behaviour problems were less than those of her brother, but she did have attacks of screaming.

#### *Progress*

There has been no change in her condition during the last 2 years. On her last out-patient visit, she was found to be using the aphakic part of her pupils, and an aphakic correction was prescribed. With right +8 D sph., and left + 9 D sph., the visual acuity is 6/24 in each eye, and she wears glasses happily.

**Case 4, a girl aged 5 years**, was noted to have a red left eye while she was an in-patient at the Queen Elizabeth Hospital for Children, Hackney, for gastroenteritis in January, 1970. There was a vague history of a blunt injury to this eye 2 weeks previously. She was born at full term and was the mother's second pregnancy at the age of 34 years. She was delivered by forceps because of

maternal distress, the birth weight being 6 lb. 11 oz. The neonatal period was uneventful, but the milestones of early childhood were delayed. At the age of 1 year, she was treated for a spontaneous fracture of the femur. There was no family history nor parental consanguinity.

#### *Examination*

The left eye was obviously injected, but full examination was not possible in the out-patient department because of lack of co-operation, and an examination under anaesthesia was carried out subsequently.

The left cornea was oedematous, the anterior chamber shallow but present, and the pupil semi-dilated and fixed. The lens was subluxated downwards and temporally, and was tilted forward into the anterior chamber, firmly caught by the pupillary margin. The ocular tension was 28 mm. Hg (Schiötz). There was no clear view of the fundus.

The right eye was white, and on dilatation of the pupil the right lens was found to be subluxated downwards and temporally. The ocular tension in this eye was 14 mm. Hg (Schiötz) and the fundus was normal.

General features were typical of homocystinuria (see Table). The child had gross mental retardation, but was very excitable. Her speech was severely retarded and her vocabulary (at the age of 6 years) consisted of "mum" and "Maria". X ray shows generalized osteoporosis. Examination of other systems gave negative results.

#### *Treatment and progress*

Local steroid drops and acetazolamide were given and to this treatment she responded dramatically in that the left eye became white, the anterior chamber deepened, the pupil contracted, the lens fell back into its normal position, and the tension became normal. Gutt. pilocarpine 1 per cent. three times a day were then started. The eye remained white and the tension normal for one week, but the lens then again dislocated partly into the anterior chamber with secondary glaucoma. Medical treatment was not successful, and surgery was indicated. It was thought that there was an element of pupillary block, but a peripheral iridectomy failed to control the tension. Aspiration of clear lens matter was then performed under magnification. The operation was uneventful and there was no vitreous loss. The postoperative period was rather prolonged with anterior uveitis which cleared in about 6 weeks on local treatment with atropine and steroid drops.

At the present time, the patient's condition remains unchanged. The right lens remains subluxated. Contact lens fitting for the aphakic left eye is out of the question and has not been attempted.

#### **Discussion**

Spiro, Schimke, and Welch (1965) described a case of schizophrenia in a patient suffering from homocystinuria. They postulated that there might well be a relationship between these two conditions. Case 1 in the present series is so far the second recorded case of this association, and is, therefore, of some interest.

The classical signs of Marfan's syndrome have been described in a few patients suffering from homocystinuria, but none in this series showed these features. Marchesani's syndrome is even more rarely associated with homocystinuria, although Presley and others (1969) described two cases. In the present series, Case 2 has features resembling Marchesani's syndrome, with short pyknotic build, strong musculature, short neck, tight joints, and spherophakia. Indeed, he was originally diagnosed as a case of Marchesani's syndrome before the biochemical abnormality was detected.

Skeletal abnormalities which have been described include osteoporosis, pes cavus, and genu valgum. Of the four cases in this series, only one (Case 4) has definite osteoporosis, and the spontaneous fracture of femur she had suffered at the age of one year is probably explained by this bony abnormality.

Garston, Gordon, Hart, and Pollitt (1970) described a case of homocystinuria complicated by optic atrophy. This complication was not seen in any of the four cases of the present series.

All the four cases described suffer from mental retardation. Case 3 is the least affected, but she is the youngest in the series. This agrees with the findings of most authors, although the report of sixteen patients of normal intelligence in a series of 38 cases by Schimke, McKusick, Huang, and Pollack (1965) seems to be unusual.

### Summary

Four cases of homocystinuria have been described, one of which also suffers from schizophrenia. A relationship between these two conditions is re-emphasized. Another case showed some of the features of Marchesani's syndrome.

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