PUPIL-BLOCK GLAUCOMA IN HOMOCYSTINURIA*†

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HOMOCYSTINURIA is an inborn error of metabolism due to deficiency of the enzyme cystathionine synthetase. This results in an increased excretion of homocystine in the urine and raised homocystine and methionine levels in the blood and cerebrospinal fluid.

Clinically there is a picture of ectopia lentis, due to zonular degeneration, skeletal changes, fine fair hair, shuffling gait, mental retardation, and thrombo-embolic episodes. The first and last of these findings can pose very difficult problems for the ophthalmologist as will be seen from the reported cases.

The mode of inheritance of this condition is known to be of the autosomal recessive type. It was first described by Field, Carson, Cusworth, Dent, and Neill (1962) in Northern Ireland and a clinical and pathological review of ten cases was made in 1965. All had ectopia lentis. Several cases have since been described in the United Kingdom and United States of America, and since 1965 four further cases have been discovered in Northern Ireland.

Three of these first presented as ophthalmological problems with pupil-block glaucoma. A previously described case reported by Arnott and Greaves (1964) has since had bilateral lens extractions for pupil-block glaucoma, and another case described as Marfan's syndrome with bilateral secondary glaucoma (reported by Martin and Cowan, 1960) is reviewed. Lieberman, Podos, and Hartstein (1966) described two cases in which the history and findings of bilateral dislocation of the lenses associated with pupil-block glaucoma led to the recognition of homocystinuria.

In five cases described in this paper nine eyes had this condition and six lens extractions were carried out. The following case histories illustrate the difficulties in treatment and management.

Case Reports

Case 1, a boy born on October 21, 1957, was referred to a paediatrician in 1962 because of backwardness and was discovered to have homocystinuria. An ophthalmic opinion was first sought in October, 1963 when bilateral ectopia lentis was confirmed, the lenses appearing to be very spherical with resulting myopic astigmatism. This boy had all the typical clinical features of homocystinuria, which have been fully documented by Arnott and Greaves (1964).

In January, 1965, he presented with a history of a painful left eye for 4 weeks, and was found to have glaucoma secondary to complete dislocation of the lens into the anterior chamber. The intra-ocular pressure rapidly returned to normal on Diamox and he was started on Heparin 1,500 units 8-hourly. Gutt. Eserine were used as the lens had fallen back into position.

* Received for publication February 28, 1967.

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Operation.—The following day the cornea was seen to be hazy, the eye hard, and the lens behind a miotic pupil. One drop of 10 per cent. Phenylephrine was instilled, the pupil was dilated, and the lens immediately came forward into the anterior chamber. An *ab externo* incision was used, broad iridectomy was carried out, and a vectis was used for extracting the lens without vitreous loss. Six corneo-scleral sutures of virgin silk were used to close the wound. A small hyphaema was present at the end of the operation.

Postoperative recovery was normal with the hyphaema clear at the first dressing. Heparin was continued for 2 weeks.

Progress.—At the end of April, 1965, he was crying and very restless with a 2-day history of a red watery right eye. The intra-ocular pressure was raised, the cornea hazy, and the pupil dilated.

He was admitted to hospital, and was given anticoagulants as previously and Diamox. Eserine was used as soon as the lens fell back into position, and 4 days later a right lens extraction was carried out without vitreous loss, by similar technique to that used with the left eye. He made an uneventful postoperative recovery and no hyphaema occurred.

Result.—One month later the eye was quiet and both fundi appeared normal. He was supplied with +10 lenses but has never worn them for any length of time.

Since then he has had episodes of chest infection and serious cardiac failure, the latter necessitating hospital treatment for nearly 2 months.

The eyes were last examined in November, 1966. They had remained quiet and despite not wearing glasses the patient appears to see reasonably well.

Family History.—There is an affected sister born on October 10, 1960, who was documented by Arnott and Greaves (1964). She has bilateral ectopia lentis with shallow anterior chambers, but appears to see well, and has had only one episode of sore red eye lasting only one day.

Case 2, a woman born on October 7, 1939, was first seen in April, 1965, in the Eye Casualty Department with a 2-week history of blurred vision and pain in the left eye. She had been vomiting for one day. There was no previous history of visual trouble. The visual acuity was 6/24 in the right eye and counting fingers in the left.

Examination.—The right anterior chamber was shallow, and the pupil reacted to light. The left cornea was hazy, the anterior chamber shallow, and the pupil fixed and dilated. The intra-ocular pressure was raised in both eyes. The patient was admitted as a case of acute narrow-angle glaucoma and treated with intensive miotics and Diamox. The right intra-ocular pressure fell to normal in an hour and the left was normal by the next morning though the pupil stayed dilated.

Diagnosis.—It was noticed that she had bilateral ectopia lentis and had features suggestive of homocystinuria, *i.e.* fine hair, malar flush, arachnodactyly, genu valgum, livido reticularis, a shuffling gait, and a low I.Q., and the diagnosis was confirmed biochemically.

She continued to be treated medically and was discharged 2 weeks later having refused surgical treatment. In the next year she suffered several attacks of pain in both eyes but did not attend hospital.

Result.—She was last seen at home in November, 1966. Her mother said that she suffered occasional headaches and attacks of a painful right eye which did not last long, and that she rarely went out of the house. The visual acuity was counting fingers in each eye. Both lenses were cataractous and dislocated into the anterior chambers, and the pupils were fixed and dilated. There were ciliary staphylomata, most marked above and greater in the left than in the right eye. The ocular tension felt normal on palpation.

Family History.—One brother who died aged 6 years was short-sighted and mentally retarded, and there were four unaffected brothers and one sister. There was also one affected brother, who had bilateral ectopia lentis with iridodonesis, and very high myopia, but no attacks of redness and pain.

It is of interest that a maternal uncle with congenital cataracts has eight children aged from 1 to 16 years, all with bilateral congenital cataracts, but that tests for homocystinuria have proved negative.

Case 3, a young man born on October 10, 1947, was first seen by an ophthalmologist in November, 1960, when bilateral subluxated lenses were diagnosed. It was felt that poor vision accounted for his so-called stupidity and backwardness. No skeletal abnormality was found and myopic glasses were ordered.

He was next seen in July, 1965, with a history of a painful right eye, vomiting, and fits for 3 days. He had previously been investigated for fits but no cause was found.

Examination.—The right cornea was hazy with the lens impacted in a dilated pupil. Left iridodonesis was present. Arachnodactyly, genu valgum, and low intelligence were noted. Blood pressure was recorded as 200/105.

Treatment.—A presumptive diagnosis of homocystinuria having been made, he was admitted to hospital and started on miotics and Diamox and Heparin 12,500 u. intravenously followed by 10,000 u. 8-hourly.

After oral Glycerol and intramuscular Diamox, surgery was carried out the next day. An *ab externo* incision was made, and peripheral iridotomy and intracapsular extraction with forceps were done without vitreous loss. The incision was closed with six corneo-scleral sutures of virgin silk.

Progress.—The eye appeared normal at first dressing, but the blood pressure and blood urea rose, and there was vomiting and haematemesis. On the fourth postoperative day there was a total hyphaema and a large haematoma in the left thigh—the site of the premedication injection.

The patient was transferred to a medical ward on the eighth postoperative day, as the blood pressure had risen to 200/150 and the blood urea to 274 mg. per cent. These fell on hypotensive treatment but the haemoglobin fell to 39 per cent., and transfusion of several pints of blood was needed. Subcutaneous heparin 7,500 units twice daily was continued for several months, and the haematoma and hyphaema took several weeks to clear.

Result.—The patient was last seen in October, 1966, when the right eye was quiet and the fundus normal.

The right aphakic correction was $+14.0/+1.0 \times 165 = 6/18$.

The left myopic correction was $-14.0/-2.0 \times 75 = 6/24$.

He preferred the aphakic correction.

Family History.—He was an only child. A cousin on his father's side now dead was said to have had dislocated lenses.

Case 4, a male premature infant born on March 29, 1959, weighing 3 lb. 5 oz., was first referred to an ophthalmic hospital in March, 1963, because of defective vision when he was 4 years old.

Examination.—He was refracted under atropine and found to be highly myopic. Glasses -14 D sph. both eyes were ordered. The fundi were reported as normal in appearance. He was twice refracted under atropine in the following 18 months when increasing myopia was found, but ectopia lentis was not noted. His appearance was normal but his intelligence was below average and a paediatrician diagnosed mild cerebral palsy.

Progress.—In March, 1966, he developed severe pain in the right eye, and was seen by an ophthalmologist who noted a hazy cornea, pupil dilated, and lens partially in the anterior chamber. The eye was very hard. The left lens was also dislocated but no iridodonesis was present. The ocular tension fell to normal on Diamox and the pupil was constricted after the lens fell back into position. Homocystinuria was suspected and was confirmed by urine testing and serologically. He was discharged home on miotics.

At the beginning of April the lens came forward again during an out-patient examination but it fell back when the patient lay down. The pupil was constricted and miotics were increased.

Treatment.—It was now felt that surgery was necessary and he was admitted to hospital at the beginning of May, and started on subcutaneous Heparin 5,000 units twice daily. Diamox was given intramuscularly before and intravenously during surgery. After an *ab externo* incision and broad iridectomy, a right intracapsular extraction was carried out with a vectis. There was considerable vitreous loss. At the first dressing a complete hyphaema was present, but this cleared in a week and the post-operative course was otherwise uneventful.

Progress.—At the beginning of June it was reported that the left eye had been red for 3 days but without pain. The pupil was dilated, with the lens in the anterior chamber, but the tension was normal. As with the other eye the lens fell back when the patient lay down, and the pupil was constricted with miotics.

Despite the continuous use of miotics the lens came forward again at the end of June and this time the ocular tension was greatly raised, and there was pain and vomiting. He was again admitted to hospital and the intra-ocular pressure was reduced to normal with Diamox.

Treatment.—Anticoagulation was started with Heparin and continued for 2 weeks, and surgery was carried out the day after admission. Oral glycerol and intra-muscular Diamox were used pre-operatively and Diamox intravenously during the operation. Flieringa's ring was used and after an *ab externo* incision and broad iridectomy intracapsular extraction was carried out with a vectis. Despite precautions there was again considerable vitreous loss, but the postoperative recovery was uneventful.

Result.—In October, 1966, the visual acuity was 6/9 with aphakic correction in each eye. He reported back in December, 1966, with a right retinal detachment.

Family History.—His younger brother and twin sister were normal.

Case 5, a young man born on March 2, 1949, was reported by Martin and Cowan (1960) as a case of Marfan's syndrome. The left eye had been enucleated in 1959, because it was blind and painful with ciliary staphyloma and high ocular tension. One month later the right lens was extracted with a vectis after pupil-block glaucoma. There was some vitreous loss.

Review.—In 1962 he was found to have some of the typical signs of homocystinuria: fine hair, malar flush, and livido reticularis on the extensor surfaces of the legs, pes cavus, and low I.Q. (50).

Progress.—The right visual acuity has remained since 1959 at 6/12 and N. 10 with aphakic correction. The fundus appears normal apart from slight pallor of the optic disc. The patient was last seen in November, 1966.

Family History.—He has five normal brothers and sisters and two siblings who died early from measles and "convulsions". A paternal aunt was said to have had a child like the patient, who had died at the age of 17 years.

Discussion

Cases 1 to 4 had anticoagulation treatment during and after surgery. This was felt to be necessary as five of the ten patients previously described in Northern Ireland have had major thrombo-embolic episodes (in two this caused death, one after lens extraction). Another case described by Kromrower and Wilson (1963) also died from pulmonary embolus after lens extraction.

Duthie (1965) described a patient who died on the third day after lens extraction. McDonald, Bray, Field, Love, and Davies (1964) showed that all children with homocystinuria had a greatly increased platelet stickiness, though the platelet counts were normal; this is compatible with an increased tendency to intravascular thrombosis.

However, Shimke, McKusick, Huang, and Pollock (1965), in a review of 38 cases of homocystinuria in the U.S.A., found no abnormality of clotting and platelet stickiness. There was a high incidence of intravascular thrombosis, possibly due to changes in the walls of the blood vessels. Henkind and Ashton (1965) stressed that medical management should be given every opportunity to succeed, and that surgery should be the last resort because of the grave risk of thrombo-embolic phenomena.

Anticoagulation, however, is not without its dangers and in Case 3 was probably the cause of the total hyphaema and haematoma of the thigh. It perhaps also predisposed to hyphaemata in Cases 1 and 4.

It is interesting to note that although Case 4 was seen by an ophthalmologist in 1963 and 1964, bilateral ectopia lentis and therefore homocystinuria was not diagnosed till 3 years later. Unlike Case 1, Case 2, and the sister of Case 1, he did not have iridodonesis and clinical features typical of homocystinuria were not present. However, all the patients described were highly myopic, probably because the lens is smaller and rounder than normal and is not in the usual position in the eye.

Gaull and Gaitonde (1966) reported that the left lens of Case 1 was spherical rather than lens-shaped. Cystathionine synthetase activity, previously shown to be absent from the liver and brain in homocystinuria, was present in the optic lens.

Prof. Norman Ashton has reported on four eyes from three patients, one of whom was Case 5. The zonular fibres showed degenerative changes on both light and electron

microscopy. There was thickening of these fibres with retraction, and fusion with the much thickened basement membrane of the non-pigmented ciliary epithelium.

Six intracapsular lens extractions were carried out on four patients (Cases 1 and 3 to 5); vitreous was lost in three and one retinal detachment has so far been observed after follow-up periods of from 3 months to 7 years.

Case 2 illustrates the end-result in pupil-block glaucoma when no surgical treatment has been carried out.

The hazards of surgical treatment of anterior dislocation of the lens are well known. Chandler (1964), discussing the choice of treatment in such cases, stressed the frequency of vitreous loss and the tendency to detachment. Discussion of the lens is not easy, two to four operations being usually needed using two needles, but he regarded that this is a fairly safe procedure in comparison with intracapsular extraction. With the lens in the anterior chamber or impacted in the pupil causing pupil block, the lens may go back spontaneously or with the use of mydriatic drugs as in Cases 1 and 4. Chandler advocated an iridotomy or iridectomy or even simple transfixion to relieve the pupil block and therefore the glaucoma. He stated that if the eye maintained useful vision there was no need to remove the lens.

This method was used successfully by Lieberman and others (1966) in a case of homocystinuria, but retinal detachment may occur, even when the lens extraction is not carried out, as a case of homocystinuria reported by Carson, Dent, Field, and Gaull (1965).

Yet many authors suggest immediate lens extraction as the treatment of choice in cases of anterior dislocation of the lens causing glaucoma, provided suitable precautions are taken (Becker, 1961; Sugar, 1964; Stallard, 1965).

From January, 1965, to December, 1966, when the first four of these patients were seen and treated as cases of homocystinuria with pupil-block glaucoma, two new cases of Marfan's syndrome with bilateral ectopia lentis were also seen at the Eye Department in Belfast. Neither of these required surgery. During the same period four cases of anterior dislocation of the lens without homocystinuria were operated on for removal of the lens; three of these were traumatic and one was due to a shrunken hypermature lens.

Summary

Fourteen cases of homocystinuria have been discovered in Northern Ireland. All had ectopia lentis though not all the other clinical features of homocystinuria were present.

Five cases with acute pupil-block glaucoma are described, three of which presented with this condition before homocystinuria was diagnosed.

Four of these patients underwent six lens extractions and in one case surgery was refused. The difficulties of management and surgery are discussed.

I should like to thank Dr. C. M. B. Field for his advice and encouragement, and Mr. J. A. Corkey, Mr. V. A. F. Martin, Mr. R. H. Baird, and Mr. E. C. Cowan for permission to publish details of their cases.

ADDENDUM

The following cases of homocystinuria have been discovered during September, 1967, viz. three affected children in a family of six.

Case 6, a girl born on September 27, 1957, is mentally retarded and tall for her age, with fine fair hair, arachnodactyly, and genu valgum. She first visited an ophthalmologist in 1961 with bilateral ectopia

lentic and was diagnosed as a case of Marfan's syndrome. She had an acute attack of pupil-block glaucoma in the right eye in May, 1965, complicated by iritis. In July, 1965, a right cataract extraction was attempted, but there was vitreous loss and posterior dislocation of the lens. In March, 1966, she had an acute attack of glaucoma in the left eye and later an injection of retrobulbar alcohol was given.

At present she appears to see reasonably well with her right eye which has normal intra-ocular pressure, the lens being dislocated downwards and backwards into the vitreous. The left eye is blind and grossly buphthalmic.

Case 7, a girl born on October 30, 1962, has general clinical features of homocystinuria with bilateral ectopia lentis, the lenses being subluxated upwards and nasally. The eyes otherwise are normal. Both anterior chambers are very shallow. No iridodonesis is present.

Case 8, a boy born on October 21, 1966, has fine fair hair but no other typical clinical features of homocystinuria. The eyes are normal with no signs of ectopia lentis and he is mentally normal for his age.

Two interesting points arise from these children, all of whom have biochemically proven homocystinuria:

(1) All three have had increased platelet stickiness which has been reduced by 80 to 90 per cent. by large doses of Vitamin B 6. This work has still to be fully assessed but may be of importance in the prevention of thrombo-embolic episodes.

(2) The youngest child is the only one in the series in Northern Ireland, now seventeen in number, without ectopia lentis.

Furthermore, Komrower, Lambert, Cusworth, and Westall (1966) reported a child at aged 2 years 3 months who was in excellent health apart from genu valgum, the I.Q. being 97 and the eyes normal, and Perry, Dunn, Hansen, MacDougall, and Warrington (1966) reported a child aged 6 months in which slit-lamp examination revealed no ocular abnormality.

It is likely that these cases represent an incomplete clinical form of the disease but it will be interesting to see if the lenses subluxate as they grow older.

I am indebted to Mr. W. L. Robinson for the previous ophthalmic history of Case 6.

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