

An unusual case of homocystinuria

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Homocystinuria, an inborn error of amino acid metabolism, was discovered independently by Carson and Neill (1962) and Gerritsen, Vaughn, and Waisman (1962). The ocular manifestations have been well described by Presley and Sidbury (1967).

A boy aged 8½ years presented with a 2-week history of an irritable bloodshot left eye after being injured by a snowball.

The eye was injected and there was an area of corneal oedema where the lens was in contact with the posterior corneal surface. The lens was dislocated antero-inferiorly and the intraocular pressure appeared to be raised on digital examination. Externally the other eye appeared normal.

The patient was admitted to hospital and treated with topical steroids and Diamox. A mydriatic trial was performed on the right eye to investigate zonular function, and the anterior chamber became appreciably shallow through anterior displacement of the lens. Mydriatics were discontinued and miotics were substituted; these were required for 2 days before the anterior chamber deepened to its pre-test state. The intraocular pressure was at no time raised in this eye.

Following this test, a provisional diagnosis of homocystinuria or Marfan's syndrome was made. Examination of the urine (R.J.P.) revealed a strongly positive cyanide nitroprusside test. Amino-acid chromatography and electrophoresis confirmed the presence of homocystine in the urine.

General examination (R.R.G.)

The patient was a pleasant mentally-retarded boy, 49" in height and weighing 4 stone (Fig. 1). His hair was brown and there was no malar flush. He had severe genu valgum (Fig. 2), more pronounced on the right side with surgical scars over the inner aspects of the knee joints. There was also pes planus. He had a characteristic "Chaplinesque" gait and walked with his arms in a bowed position because of stiff upper limb joints. There was a *café au lait* spot in the right groin, bilateral femoral bruits, and absent dorsalis pedis pulses. Blood pressure 100/70. Electrocardiogram normal.

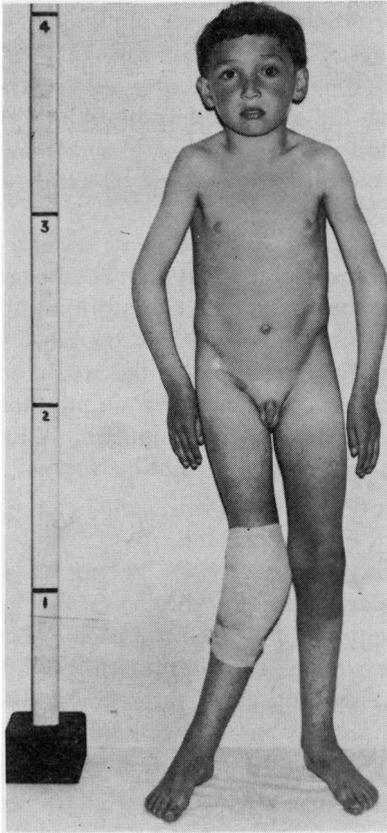
Past history and family history

The mother had noted her son's eyes "shimmering" for some years. At 2 years old he had been seen by an orthopaedic surgeon because of late walking. Bilateral genu valgum was thought to be due to late rickets and was treated surgically. At 4 years radiological and biochemical studies were performed because a metabolic defect was suspected. Calcium and phosphorus metabolism was normal. Amino-acid chromatography showed "moderate amounts of glycine and serine, small amounts of histidine and alanine—a normal pattern". At 6 years he was operated on for tongue-tie in view of his defective speech. There was no improvement and his I.Q. was found to be 56. At 8 years he underwent further orthopaedic surgery.

The boy is the third child of unrelated white parents. They and three siblings (one newborn girl, two brothers) have been examined, but there is no biochemical or physical evidence of homocystinuria. One other sibling was postmature and died on the day of birth.

Ocular surgery

In view of the persistent dislocation of the left lens, with corneal contact, and continuing irritability of the eye, it was decided to remove the left lens. 25 g. oral glycerol was given preoperatively and general anaesthesia used. A conventional *ab externo* incision was made. The iris was found to be adherent to the posterior corneal surface above and a broad iridectomy was performed. Cryo-extraction of the lens in capsule was carried out with some vitreous loss. To prevent vascular complications, intravenous heparin 20,000 units was administered at the time of operation and for 3 subsequent days.

FIG. 2 *Genu valgum*FIG. 1 *General appearance*

Postoperative recovery was uneventful. The eye remained irritable for about 10 days and was treated with local mydriatic and steroid drops. There was a marked vitreous haze which obscured all fundus details for one month. On subsequent fundus examination, marked left optic atrophy was discovered. The retinal vasculature was attenuated and the peripheral retina thin and atrophic. The left eye is completely blind. The right eye sees 6/18 with -16 D sph., $+4$ D cyl., axis 90° .

Gonioscopy

Both angles are open with multiple fine iris processes and marked pigmentation of Schwalbe's line. The angles are abnormal compared with those of the two brothers.

Discussion

The diagnosis of homocystinuria depends on characteristic ocular findings, physical appearance, and biochemical abnormalities.

(a) CHARACTERISTIC OCULAR FINDINGS (Arnott and Greaves, 1964) emphasized the characteristic dislocation of the lens. This is inferior in direction in contradistinction to other disorders such as Marfan's syndrome, Marchesani's syndrome, and congenital ectopia lentis.

The patient in the present report is of interest in that the dislocation was at first considered to be due to external trauma and not to homocystinuria. However, the ease with which dislocation was produced in the contralateral eye raised the possibility of a metabolic defect as the primary lesion. The mydriatic test in the right eye was not entirely free of risk—witness the fact that miotic therapy was required for 2 days before the anterior chamber returned to a normal depth.

Reports of optic atrophy and changes in the retinal vasculature are limited. Presley and Sidbury (1967) described two Negro siblings and one white girl with bilateral optic atrophy. Mukuno, Matsui, and Haraguchi (1967) described one case with retinal angi sclerosis and white sheath formation along the arterioles. Wilson and Ruiz (1969) described a 6-year-old Negro boy who developed bilateral acute glaucoma, and in whom examination under general anaesthesia one month later revealed bilateral central retinal artery occlusions with optic disc pallor.

The optic atrophy and retinal vessel attenuation in the present case are also complicated by the previous history of trauma. In the absence of marked pigmentary scarring at the posterior pole, it may be concluded that the metabolic defect was primarily responsible. In view of the vasculitis affecting the lower limbs, it is possible that the blood vessels to the optic nerve and retina are similarly involved. Furthermore, the secondary glaucoma which was undoubtedly present before operation may have been an additional factor in the development of optic atrophy although the disc was not cupped. Wilson and Ruiz (1969) expressed similar views regarding the aetiology of the optic atrophy.

(b) PHYSICAL APPEARANCE The malar flush, blonde hair, genu valgum, and mental deficiency have been described (Carson, Dent, Field, and Gaull, 1965). If the appearance is atypical, the diagnosis of homocystinuria may not easily be made. Our patient has brown hair and no evidence of malar flush. Furthermore, the genu valgum was noted to be markedly progressive and required multiple orthopaedic procedures; the progressive nature of genu valgum in homocystinuria has not hitherto been described.

40 per cent. of cases of homocystinuria develop fatal thromboses (Carson, 1969) commonly after general anaesthesia. This patient has had general anaesthesia on six occasions, but has shown no sign of thrombosis in spite of lower limb vasculitis.

(c) BIOCHEMICAL ABNORMALITY The urine at the age of 4 years was said to have a normal pattern. It is obvious therefore that homocystine in the urine may not always be detected. The amount excreted may be small (as little as 50 mg. per day) depending on protein intake and possibly on the amount converted to other metabolites.

The presence of homocystine in the urine may be suspected when there is a positive cyanide nitroprusside test. This test is also weakly positive in the presence of raised cystine levels, which commonly occur in heterozygous carriers of certain types of cystinuria. Because of this, low levels of homocystine in the urine giving a weak positive test may be missed or misinterpreted.

The most reliable indication of homocystine in the urine is its demonstration by electrophoresis or chromatography. A useful one-dimensional separation can be achieved using high voltage electrophoresis at pH2 after conversion of the homocystine to homocystic acid by hydrogen peroxide oxidation. Normal urine gives no detectable homocystic acid but it is quite obvious in patients with homocystinuria even at low levels of excretion.

Medical treatment

On normal diet, the patient excreted 3 mg. methionine and 18 mg. homocystine per g. urea. Plasma levels of methionine and homocystine were 1.4 and 3.0 mg./100 ml respectively (Fig. 3, opposite).

After 2 weeks' low methionine diet (based on lentils and gelatine with cystine supplements) with pyridoxine, the plasma methionine fell to 0.8 mg./100 ml. and the plasma homocystine to 0.3 mg./100 ml.

Owing to home circumstances, it was difficult to continue dietary treatment. He was maintained for some time on 50 mg. pyridoxine/day. On this treatment, the plasma

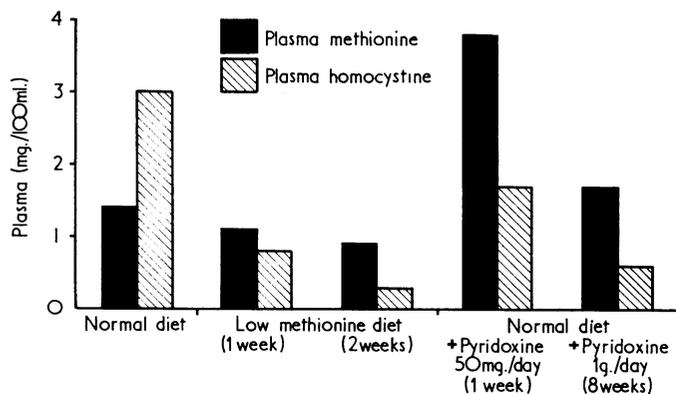


FIG. 3 Effects of treatment on plasma methionine and homocystine

methionine returned to 3.8 mg./100 ml., and the plasma homocystine to 1.8 mg./100 ml.

As Carson and Carré (1969) have recently recommended the use of large doses of pyridoxine, he was then given 1,000 mg./day of pyridoxine, and on this treatment the plasma methionine was maintained at 1.6 mg./100 ml. and the plasma homocystine at 0.6 mg./100 ml. Treatment with pyridoxine has thus reduced homocystine levels.

Summary

An 8½-year-old white boy with homocystinuria is described. The condition remained unrecognized until the left lens dislocated after an injury. The diagnosis of homocystinuria should be borne in mind even when the lens appears to dislocate because of trauma.

The lens was removed but the eye remained blind because of optic atrophy. The aetiology of optic atrophy in homocystinuria is discussed.

The boy survived six operations without thrombosis, although he had vasculitis.

The progressive nature of genu valgum in homocystinuria is described.

Pyridoxine, 1,000 mg./day considerably reduced the plasma homocystine levels.

This patient was under the care of Mr. A. Stanworth, to whom we are grateful for permission to publish case details and for helpful comments in the preparation of this paper.

References

- ARNOTT, E. J., and GREAVES, D. P. (1964) *Brit. J. Ophthalm.*, **48**, 688
 CARSON, N. A. J. (1969) *Brit. J. Hosp. Med.*, **2**, 439
 ——— and CARRÉ, I. J. (1969) *Arch. Dis. Childh.*, **44**, 387
 ———, DENT, C. E., FIELD, C. M. B., and GAULL, G. E. (1965) *J. Pediat.*, **66**, 565
 ——— and NEILL, D. W. (1962) *Arch. Dis. Childh.*, **37**, 595
 GERRITSEN, T., VAUGHN, J. G., and WAISMAN, H. A. (1962) *Biochem. Biophys. Res. Commun.*, **9**, 493
 MUKUNO, K., MATSUI, K., and HARAGUCHI, H. (1967) *Acta Soc. ophthal. jap.*, **71**, 66
 PRESLEY, G. D., and SIDBURY, J. B. (1967) *Amer. J. Ophthalm.*, **63**, 1723
 WILSON, R. SLOAN, and RUIZ, R. S. (1969) *Arch. Ophthalm. (Chicago)*, **82**, 267

Addendum

December 11, 1969 The right lens dislocated spontaneously into the anterior chamber. The patient was placed flat in bed and given Diamox 125 mg. twice daily. The pupil was dilated with gutt. Phenylephrine 10 per cent. and after one day the lens replaced itself behind the iris. The pupil was immediately constricted with gutt. Pilocarpine 4 per cent. and is now permanently miosed with the aid of gutt. Pilocarpine 2 per cent. three times a day. The visual acuity has fallen to less than 6/60 in this eye with -5 D.sph.