# Homocystinuria – A Case Report

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**Introduction:**

HOMOCYSTINURIA is an inborn error of methionine metabolism, first described in 1962 by Carson and Neill[1] as a result of a survey of institutionalized mentally retarded children using urine chromatography. Mudd[2] (1964) pointed out that the defect was in a deficiency of the enzyme cystathionine synthetase which mediates the conversion of homocysteine to cystathionine (Figure 1). This he confirmed by demonstrating the deficiency of the enzyme activity in the liver of such patients.

The enzyme deficiency results in an accumulation of homocysteine. This is converted to homocystine which overflows into the urine[3]. Blood and urine levels of methionine are also increased but are usually not high enough to be detectable.

Homocystinuria is heritable in an autosomal recessive manner. Up to 1970, 150 cases have been reported in the literature[4]. The incidence among the mentally retarded is 0.3% in Ireland (Carson, 1963)[5] and 0.02% in the United States (Spaeth and Barber, 1967)[6]. Most cases have been reported among Caucasians though reports have also appeared from Japan, India[4] and Thailand[7]. We are not aware of any previously reported case in Malaysia and Singapore.

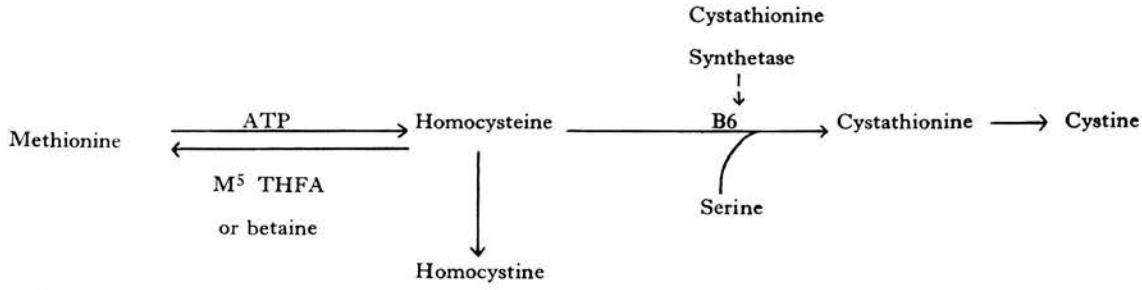
**Case report:**

A 9 year-old Chinese boy was first seen at the University Hospital, Kuala Lumpur on 17/12/74 for progressive deterioration of vision of 3 years' duration. He was variously diagnosed as having "dislocated lenses" and "enophthalmitis".

He was born after a full term normal delivery with a birth weight of 7 lbs. His developmental milestones were delayed-viz. sat up at 1 year, walked at 3 years and could say a few words with meaning only at 5 years. He was also hampered by deteriorating vision in school which he was forced to leave a year before admission to hospital.

He is the second child in a family of five. His parents were not related and there was no family

**Figure I: Methionine Metabolism in Mamalian Tissues**




$M^5THFA$ = $N^5$ methyltetrahydrofolic acid.
B6 = Pyridoxal phosphate.
ATP = Adenosine triphosphate.

history of similar illness, mental retardation, unexplained deaths or abortions. He had no past history of thrombosis.

**Physical Examination** showed the Marfan habitus (Fig. 2) – tall and thin with the height on the 50th percentile of the growth charts; arm span (139 cm) greater than height (133 cm) upper segment to lower segment ratio (64/69) 0.92 and arachnodactyly (Fig. 3). Bone deformities were striking – prominent thoracic kyphoscoliosis (Fig. 4), pectus excavatum (Fig. 5) and mild genu valgum. His fingers could not be fully extended because of contractures (Fig. 6) and there was limitation of abduction at the shoulder joints due to a varus deformity of the head of the humerus (Fig. 7).

Examination of his eyes was hampered by the marked (Fig. 8) photophobia. Divergent squint was present with blue sclerae and interstitial keratitis. There was a corneal opacity on the left eye in addition to the bilateral vitreous opacity. No ectopia lentis could be detected and the Consultant ophthalmologist was of the opinion that he had endophthalmitis.

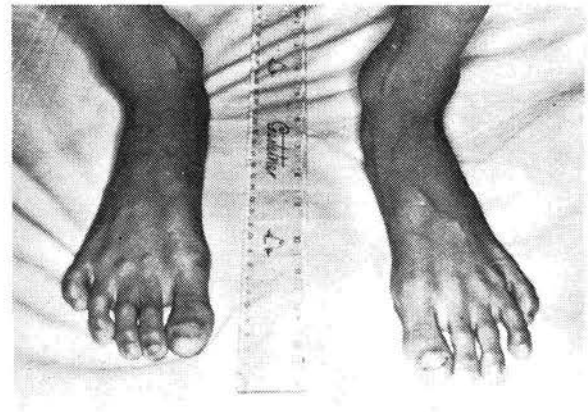


**Fig. 3 – Arachnodactyly.**

He was severely mentally retarded – could say a few words but was unable to speak in sentences. All peripheral pulses were palpable and there was no bruit heard. No skin manifestations of homocystinuria could be detected.

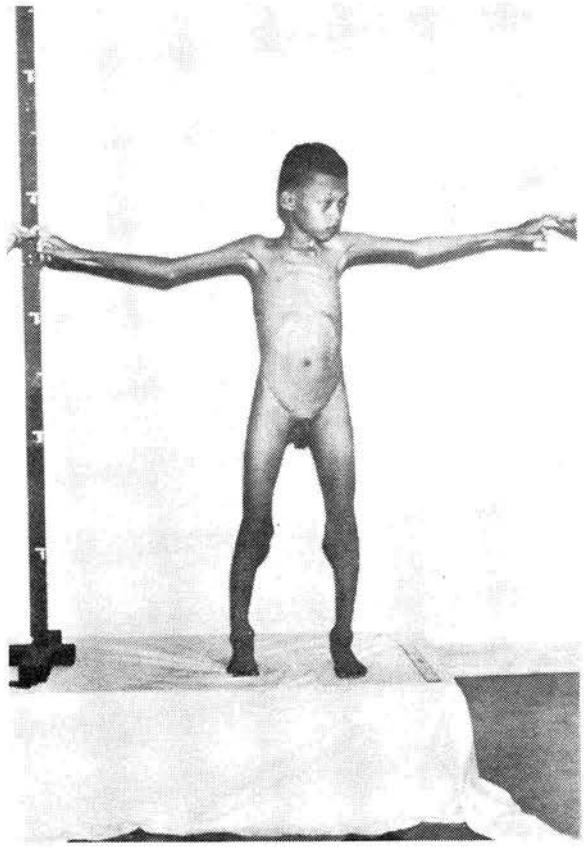


**Fig. 2 – Shows the Marfan habitus; the arm span is greater than the height.**

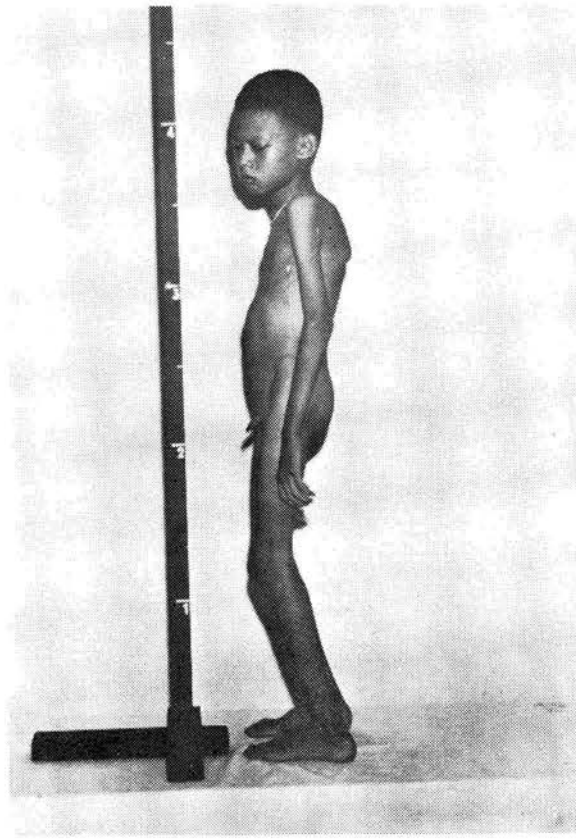


**Fig. 4 – Thoracic kyphoscliosis.**

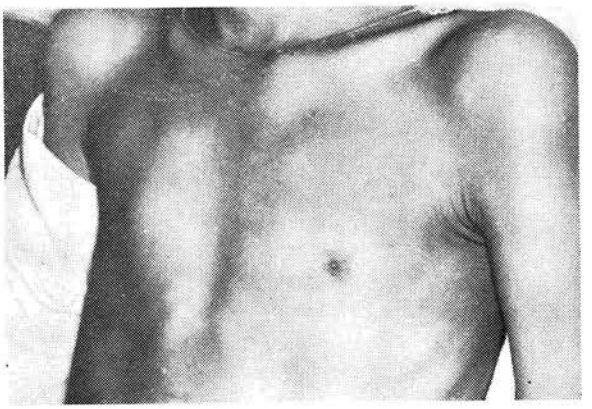


**Fig. 5 – Pectus excavatum.**

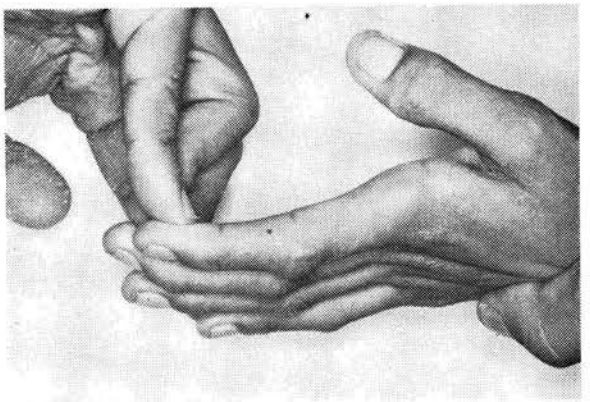


**Fig –6 Shows contractures at the proximal interphalargeal joints of the fingers thus causing limitation in extension.**

## Laboratory Studies:

Routine blood counts, urine examination, electro cardiograph and liver function tests were normal. The platelets showed a slight reduction in adhesiveness.

The cyanide nitroprusside test was strongly positive on 3 occasions. One dimensional urine chromatography in butanol: acetic acid: water (12:3:5 v/v)[8] showed a densely staining spot corresponding to the region of homocystine marker (Fig. 9). Methionine was also detected. Blood chromatography gave similar results. Further resolution using high voltage electrophoresis in acetic acid: formic acid: water (4.6:1:32.8 v/v)[23], pH 2.0, revealed strong reaction at the spot corresponding to standard homocystine (Fig. 10). The homocystine marker was obtained from homocystine thiolactone by atmospheric oxidation in the presence of ferric chloride.

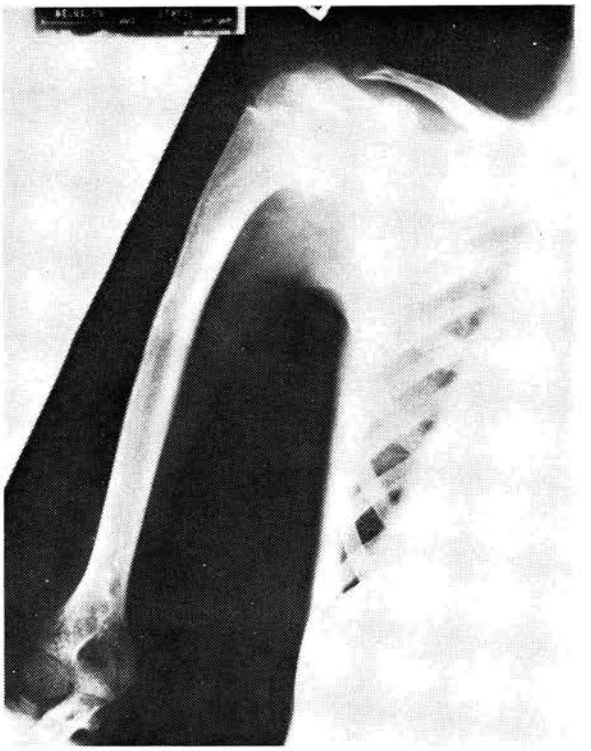


**Fig. 7 – X-Ray shows a varus deformity of the head of the left humerus.**

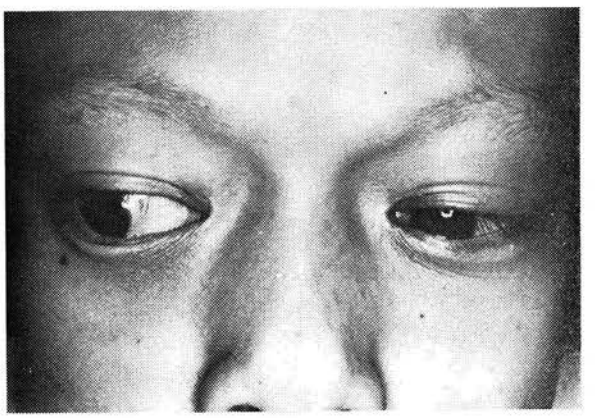


**Fig. 8 – Shows the divergent squint and a ring of blue sclera in the right eye.**

X-rays of the spine showed osteoporosis and kyphoscoliosis. The metacarpal index of 10.8 was in the Marfan range (Parish, 1966)[9]. X-rays revealed a varus deformity of the head of both humeri (Fig. 7). Serum folate level was 8 pg/ml.

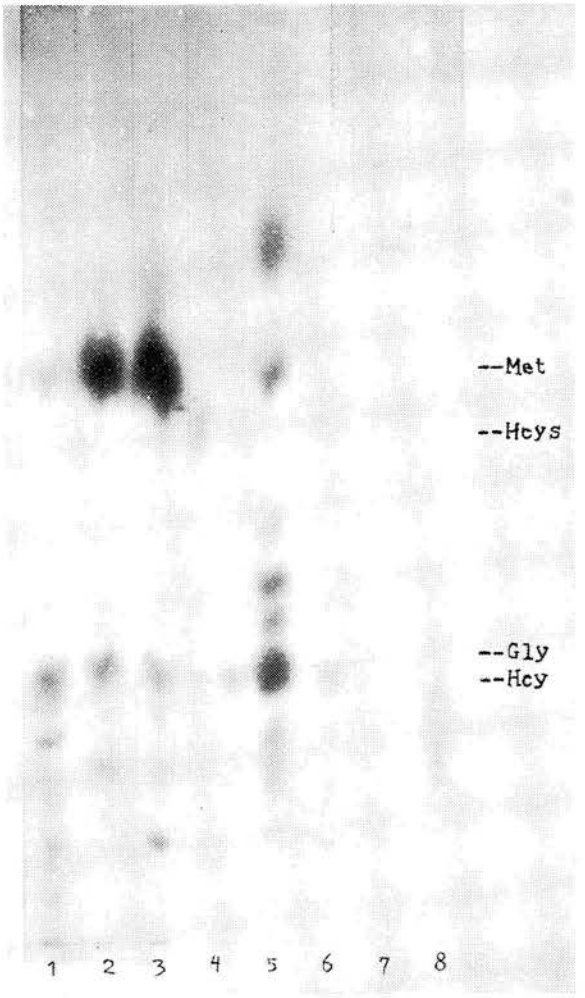



**Fig. 9 – One Dimensional Paper Chromatography of Amino Acids from the Urine of the Patient and the Parents.**

1. **Urine of Father (23.12.1974)**
2. **Urine of Mother (23.12.1974)**
3. **Urine of Patient (23.12.1974)**
4. **Standard-Mixture of 20 amino acids**
5. **Standard-Mixture of homocysteine and homocystine**
6. **Urine of Father (30.12.1974) after Methionine Loading**
7. **Urine of Mother (30.12.1974) after Methionine Loading**
8. **Urine of Patient (30.12.1974)**

**Met. = methionine; Hcys. = homocysteine; Gly. = glycine; Hcy. = homocystine**

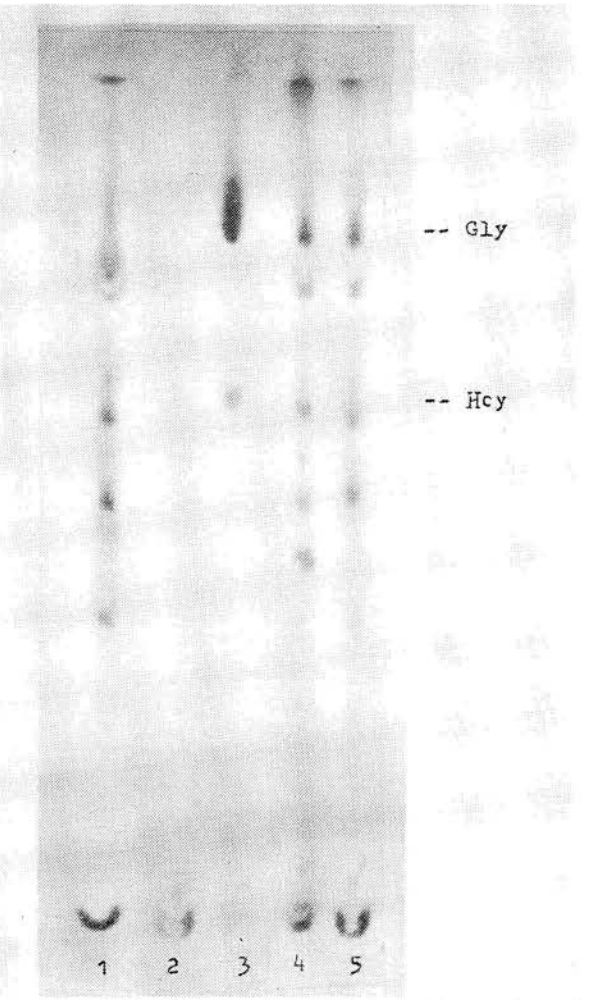



**Fig. 10 – High Voltage Electrophoretic Seperation of the Amino Acids from the Urine of the Patient and the Parents.**

1. **Urine of Father (23.12.1974)**
2. **Urine of Mother (23.12.1974)**
3. **Mixture of Homocystine and Glycine**
4. **Urine of Patient (23.12.1974)**
5. **Normal Urine to which Homocystine was added**

**Gly. = glycine; Hcy. = homocystine.**

**Family studies** were restricted to the phenotypically unaffected parents as the other siblings were not available. A methionine load (100 mg/kg) was given to the parents and 2 hours later, blood and urine samples were collected for the following tests (Table I).

## Treatment and Progress:

Large doses of Pyridoxal phosphate (600 mg daily) was given. Two weeks after therapy, the cyanide-nitroprusside test and urine chromatography still showed presence of homocystine. The serum folate level remained at 8 pg/ml. Clinically, the child remained unchanged.

**Table I**

**Biochemical Tests on the Urine Samples of the Patient and his Parents**

| | Cyanide Nitroprusside Test | *URINE* Chromatography | HVE** Confirmation |
|---|---|---|---|
| 1) *Mother:* *BEFORE* methionine loading | Faint reaction | Negative | Negative |
| *AFTER* *methionine loading | † | † | † |
| 2) *Father:* *BEFORE* methionine loading | † | † | † |
| *AFTER* *methionine loading | † | † | † |

*: methionine was given in a dose of 100 mg/Kg body weight and urine was tested 2 hours later.
†: indicates presence of homocystine.
**: HVE: High-voltage electrophoresis.

## Discussion:

The diagnosis of homocystinuria was suspected on the basis of the Marfan-like features, mental retardation and the history of "dislocated lenses".

Ectopia lentis occurs in the majority of homocystinurics. Cross and Jensen (1973)[10], in a review of 42 biochemically proven cases noted that 38 (90%) had symmetrically dislocated lenses. It is difficult to determine the time of onset of dislocation as serial examinations from birth were not performed in most series. In McKusick's series of 83 cases[11], dislocated lens was detected at 3 years of age in one child while in two others it did not occur till the ages of 24 and 28 years – the latter were mildly affected cases with minimal skeletal manifestations, unlike the patient described here. Other less well-known ocular abnormalities reported include strabismus, blue sclerae, glaucoma with or without pupillary entrapment of the dislocated lenses, buphthalmos, staphyloma, retinal detachment and optic atrophy. Cross et al (1973)[10] found 5 with strabismus and two with blue sclerae in their 42 cases. Both these features are present in the patient reported here. The striking eye changes in the patient described i.e. corneal opacity, vitreous opacity, bilateral endophthalmitis and interstitial keratitis are atypical of homocystinuria and to the best of our knowledge, have not been described.

The skeletal abnormalities, namely the Marfan habitus, kyphoscoliosis, pectus excavatum and osteoporosis are well established features of homocystinuria. The contractures of the fingers in this disorder contrast sharply against the joint laxity of the fingers seen in Marfan's Syndrome. In addition, the varus deformity of the head of the humeri is a distinctive feature of the disease.

Mental retardation, the other conspicuous finding in this patient, probably began early in life, as evidenced by the delayed developmental milestones. Though present in the majority of homocystinurics, it is not an invariable feature and intelligence may even be superior. Other nervous system manifestations described include seizures and psychoses.

Thromboembolic phenomena are commonly described in homocystinuria, especially following surgical procedures. In addition, angiographic studies are contradicted because of the risk of thrombosis. These patients are also prone to myocardial infarction, renal vascular hypertension, pulmonary and cerebral thrombosis.

No cutaneous manifestations were observed in this child. Those that have been described in homocystinuria include malar flush, livedo reticularis and light-coloured hair.

The differential diagnosis rests chiefly with Marfan Syndrome. Table II after McKusick[11] lists the contrasting features.

The cyanide-nitroprusside test, strongly positive in the patient described, is based on the reduction of cystine or homocystine in the presence of sodium cyanide to cysteine or homocysteine which then reacts with nitroprusside to give a violet colour. It is not specific for homocystinuria.

The diagnosis was established by urine and blood chromatography. Urine chromatography revealed dense staining spots corresponding to homocystine. Further resolution on high voltage electrophoresis confirmed the presence of homocystine in the patient, as well as in the parents.

**Table II**

**Differentiating features of Homocystinuria and Marfans Syndrome (after McKusik, 1972)[11]**

| | Homocystinuria | Marfan Syndrome |
|---|---|---|
| 1. Inheritance | Recessive | Dominant |
| 2. Skeletal abnormalities | Osteoporosis, fractures, arachnodactyly | Arachnodactyly and loose-jointedness more striking. |
| 3. Pectus excavatum or Carinatum | Frequent | Frequent |
| 4. *Ectopia lentis* | Develops progressively with downward displacement. | Usually congenital and displaced upward |
| 5. *Vascular disease* | Dilation with thrombosis in medium sized arteries and veins. | Dilation and/or dissection of aorta. |
| 6. *Skin* | Malar flush, livedo reticularis | Striae distensae. |
| 7. *Mental retardation* | Frequent | Absent |

Facilities for the essay of cystathionine synthetase were not available.

Detection of heterozygote carriers of this disorder is often hampered by the lack of facilities for enzyme assay. It has been shown that such carriers have approximately half the normal cystathionine synthetase activity in liver biopsy specimens (Finkelstein et al, 1964)[12]. Methionine loading tests, based on the reduced ability of carriers to metabolise methionine have been used in the detection of heterozygotes but many workers have not found them useful (Brenton et al, 1965[13]; Kennedy et al, 1965[14], Laster, 1965[15], Dunn et al, 1966[16]). However, Sardhawala et al, 1974[17] found that a study of sulphur-containing amino acids in plasma and urine after L-methionine loading is of value in the detection of heterozygotes for homocystinuria. The presence of homocystine in the urine of the parents after methionine loading, as confirmed by high voltage electrophoresis is significant and may indicate that parents are carriers of this disease.

Vitamin B6, a co-factor for cystathionine synthetase, is currently used in the treatment of homocystinuria on the basis that it increases residual cystathionine synthetase activity. Mudd (1970)[18] and Barber (1969)[19] treated homocystinuria with high doses of vitamin B6 and subsequently found homocystine not detectable in the urine. The disease is a heterogenous one and not all patients so treated will respond. It is not possible to predict which case will respond, but in general, mildly affected cases show a better response than the more severely affected ones. In the reported case here, the eye and mental changes, being already well-established, are unlikely to respond to any form of treatment. It is hoped that with treatment such complications, as thrombosis, may be prevented. One important point to note is that during treatment with pyridoxine, folate depletion may occur which may reduce the response to pyridoxine (Wilcken et al, 1973)[20]. It is thus important to ensure that adequate folate levels are maintained during treatment and when indicated, folate supplements given.

In addition, a low methionine diet has been used in the treatment of homocystinuria. The rationale is to reduce the concentration of metabolites proximal to the site of enzymic block i.e. methionine and to supplement the diet with cystine which is deficient as a result of the enzymic block. The efficacy of a low-methionine, high cystine diet has been reported (Komrower, 1966[21]; Perry, 1968[22]) in patients who have been treated from early infancy. Perry (1968)[22] gave the diet from birth to an affected sibling of a severely affected case of homocystinuria. Regular follow-up till the age of 6 years showed that the child was developing normally. Such a diet was not given to this patient as the disease is advanced and unlikely to respond to this form of treatment which is expensive and has to be supervised for prolonged periods.

Prognosis is very variable. Deaths have been reported as early 1 year as late as 89 years[11]. Morbidity may be considerable from thrombo-embolic phenomena, visual changes and intellectual deficit.

**Summary:**

A case of homocystinuria is presented and the clinical features, laboratory studies, treatment and prognosis discussed. We believed this is the first case reported in the Malaysian and Singapore literature.

**Acknowledgements:**

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