Classic homocystinuria: clinical, biochemical and radiological observations, and therapeutic outcome of 24 Saudi patients

M.A. Al-Essa,[1] M.S. Rashed [2] and P.T. Ozand [1,2]

SUMMARY We considered the clinical, biochemical and radiological findings, and response to pyridoxine (vitamin B_6) of 24 classic homocystinuric patients (15 females, 9 males) diagnosed at King Faisal Specialist Hospital and Research Centre. Common clinical findings included ectopia lentis (20 patients), skeletal system involvement (18 patients), vascular system involvement (9 patients) and mental retardation (all patients to varying degrees). A number of unusual findings were reported. The parents of 21 patients were first-degree relatives and 19 patients had at least one other family member affected by the same disease. Only 4 patients responded to pyridoxine; their methionine level decreased to almost normal range.

Introduction

Classic homocystinuria is the most common inborn error of methionine metabolism due to cystathionine β-synthase deficiency (CBS) [*1*]. It leads to significant hypermethionaemia and increased plasma total homocystine (free, disulfide and protein-bound forms). There is also increased excretion of methionine and disulfides, homocystine and cysteine-homocysteine. Infants with this disorder have non-specific complaints. After the age of 3 years, sublaxation of the ocular lenses are is [*2*], and by 7 years of age typical marfanoid features become apparent [*3*]. Affected individuals are tall and thin with elongated limbs. They have arachnodactyly, scoliosis and a fair complexion. Progressive mental retardation is common, which may be explained by repeated strokes and homocysteine neurotoxicity [*4–6*].

We aimed to increase awareness of classic homocystinuria among medical practitioners, particularly paediatricians, in Saudi Arabia in order to encourage early diagnosis.

Patients and methods

King Faisal Specialist Hospital and Research Centre is a tertiary referral centre in Saudi Arabia managing patients with diverse inborn errors of metabolism. The clinical and laboratory files of 24 patients

[1]*Department of Paediatrics;* [2]*Department of Biological and Medical Research, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.*
Received: 10/09/98; accepted: 05/09/99

who had been diagnosed as having classic homocystinuria were studied retrospectively. Excluded from the study were patients with nonclassical homocystinuria due to vitamin B_{12} deficiency (5 patients), or methylenetetrahydrofolate reductase deficiency (3 patients), and patients with high methionine levels due to liver failure.

In all the patients, the diagnosis of classic homocystinuria had been established by findings of high methionine levels in blood spots by tandem mass spectrometry (MS/MS) [7], or in plasma by high-pressure liquid chromatography and by MS/MS analysis of urine for homocystine and the mixed disulfide cysteine-homocysteine. These diagnostic findings were so sensitive and specific for the diagnosis of classic homocystinuria that we only measured cystathionine β-synthase activity in fibroblasts (revealing its deficiency) in 25% of the patients.

A special diet restricted in methionine, and combination drug therapy consisting of 200–1000 mg/24 hours of pyroxidine (vitamin B_6), 1–5 mg/24 hours of folic acid, 50–100 mg/kg per day of betaine (trimethylglycine) and a prophylactic dose of aspirin were tried in all patients.

Results

We examined the files of 24 patients with classic homocystinuria whose cases had been followed by the Inborn Error of Metabolism Section over a 10-year period (1986–96). Summarized in Table 1 are the patients' presenting symptoms, other presentations on follow-up, clinical findings in the skeletal system, central nervous system, eyes and vascular system, as well as consanguinity and other family members affected with the same disease.

Of the 24 patients studied, 21 had parents who were first-degree relatives. Female patients constituted 63% of the total, males 37%. The same disease affected one or more family members of 19 patients. At the time of the study, the age range of patients was 2–14 years. The usual presentations are described as follows: mental retardation and developmental delay, seizure disorder, ocular lens dislocation and thromboembolic phenomena.

If not treated early, the condition may result in progressive mental retardation, marfanoid features and bilateral downward dislocation of the ocular lens. Unusual findings consisted of a patient who developed severe lower gastrointestinal bleeding, a patient with type 1 diabetes mellitus (probably due to the vasculopathy associated with the disease) and another patient with severe bronchiectasis (possibly due to fibrillin degeneration) which required resection of a lobe of the lung. In all, 20 patients developed downward dislocation of the ocular lens and 18 exhibited the skeletal manifestations of the disease, 3 showing severe scoliosis.

The intelligence quotient (IQ) assessed by the neuropsychiatrist revealed that 11 patients had mild mental retardation (IQ 52–67), 11 had moderate mental retardation (IQ 36–51) and 2 had severe mental retardation (IQ 20–35). Most of the patients with moderate to severe mental retardation had not been referred early enough for effective treatment. We found 8 patients had experienced thromboembolic episodes in medium or large blood vessels. These episodes involved the brain, upper limbs, lower limbs and gastrointestinal tract.

In older patients, typical marfanoid features begin to manifest. These include dolichostenomelia (long, thin limbs), a longer arm span than body length, arachnodactyly,

Table 1 **Clinical findings in 24 patients with classic homocystinuria**

Patient	Sex	Age at presentation/ age at present	Presenting symptoms	Other symptoms on follow-up	Clinical abnormalities				Consanguinity (N)	Response to vitamin B_6
					Ectopia lentis	Skeletal system	Mental retardation	Vascular system		
1	F	6/7 years	Gangrenous changes in the right upper limb	Multiple thromboembolic attacks; lens subluxation	Yes	Normal	Moderate	Multiple vascular infarcts	Yes (2)	No
2	F	7/10 years	Delayed speech	Deterioration in school	Yes	++	Moderate	Normal	No (2)	No
3	M	1/3 years	Asymptomatic; discovered accidentally	Bilateral lens dislocation; hair loss	Yes	Normal	Mild	Normal	Yes (1)	No
4	M	3/8 years	Left lens dislocation	Right lens dislocation	Yes	++	Mild	Vascular occlusion of lower limbs	Yes (1)	Yes
5	F	3 months/ 3 years	Delayed milestones and floppiness	Squint	Yes	+	Moderate	Normal	No (4)	No
6	F	5/9 years	Limping	Left-sided haemiplegia; bilateral lens dislocation	Yes	++ (scoliosis)	Moderate	Normal	Yes (0)	No
7	F	6/20 years	Bilateral lens dislocation	Panophthalmitis	Yes	+	Severe	Brain infarct	Yes (3)	Yes
8	M	2/7 years	Mental retardation and ataxia	Chronic constipation	Yes	+	Moderate	Normal	Yes (3)	No

Table 1 (*continued*)

Patient	Sex	Age at presentation/ age at present	Presenting symptoms	Other symptons on follow-up	Ectopia lentis	Clinical abnormalities Skeletal system	Mental retardation	Vascular system	Consanguinity (N)	Response to vitamin B_6
9	M	5/14 years	Haemiplegia due to brain infarction	Severe dystonia and torticolis	Yes	++ (scoliosis)	Mild	Multiple brain infarcts	Yes (1)	No
10	F	5/16 years	Multiple brain infarcts	Seizure disorder; dystonia; acute renal failure	Yes	+	Severe	Multiple brain infarcts	Yes (1)	No
11	M	10/13 years	Seizure disorder and coma	Bilateral lens dislocation	Yes	Normal	Moderate	Normal	Yes (1)	No
12	F	4/8 years	Asymptomatic	Bilateral lens dislocation	Yes	+	Mild	Normal	No (1)	No
13	F	3/8 years	Seizure disorder with mental retardation	Lower gastro-intestinal tract bleeding	Yes	+	Moderate	Lower gastro-intestinal tract bleeding	Yes (0)	Yes
14	F	2/7 years	Thrombosis of the right iliac artery	Bilateral lens dislocation	Yes	+	Mild	Thrombosis of right iliac artery	Yes (4)	No
15	F	10/13 years	Thrombosis of the left iliac artery	Bilateral lens dislocation; thrombosis of the femoral vein	Yes	+	Mild	Multiple thrombo-embolic phenomena	Yes (3)	No
16	F	4/13 years	Abdominal pain	Bronchiectasis of the lungs; bilateral lens dislocation	Yes	+	Mild	Frequent abdominal and bone pain	Yes (1)	No

Table 1 (*continued*)

Patient	Sex	Age at presentation/ age at present	Presenting symptoms	Other symptons onfollow-up	Clinical abnormalities			Consanguinity (N)	Response to vitamin B_6
					Ectopia lentis	Skeletal system	Mental retardation	Vascular system		
17	F	7/10 years	Delayed development and mental retardation	Bilateral downward lens dislocation	Yes	++ (scoliosis)	Moderate	Normal	Yes (1)	Yes
18	F	4/9 years	Bilateral lens dislocation	None	Yes	+	Mild	Normal	Yes (1)	No
19	M	3/8 years	Abdominal pain	Type 1 diabetes mellitus	No	+	Mild	Normal	Yes (1)	No
20	F	5/8 years	Mental retardation and bilateral lens dislocation	None	Yes	+	Moderate	Normal	Yes (3)	No
21	M	2/9 years	Tonic/clonic seizure	None	No	Normal	Moderate	Normal	Yes (1)	No
22	M	6 months/ 2 years	Excessive crying; seizure	None	No	Normal	Mild	Normal	Yes (0)	No
23	M	7/14 years	Deterioration in school	Visual deterioration performance	Yes	+	Moderate	Normal	Yes (3)	No
24	F	1/4 years	Developmental delay	Severe eczema	No	Normal	Mild	Normal	Yes (0)	No

Skeletal system involvement: + Mild; ++ Moderate (± scoliosis)
(N) = other family members affected with homocystinuria

Steinberg sign and wrist sign. Ectopia lentis with myopia and occasionally glaucoma or cataracts are encountered.

The most common finding in the skeletal survey was osteoporosis, increased length of long bones, irregular and widened metaphyses and metaphysial spicules. Computed tomography (CT) scans of the brain revealed 3 patients with brain infarcts, 1 patient with superior sagittal sinus thrombosis and 7 patients with white matter changes. The electroencephalogram (EEG) was abnormal in 8 patients due to abnormal background activity and/or focal epileptic discharge present in 6 patients. Only 4 patients responded to vitamin B_6 (30 mg/kg per day). Their methionine level dropped to almost normal range after therapy.

Discussion

Homocystinuria due to CBS deficiency is a rare metabolic disorder. Since 1962, only 600 cases have been described worldwide. The cases described here thus constitute 4% of the world's CBS patient population. Only one-quarter of the cases described were detected by neonatal screening, through the finding of high methionine in blood spots of neonates. The remaining cases were detected either in high-risk families, or because of the presence of the common clinical features of the disease.

Subluxation of the ocular lens in homocystinuric patients is usually diagnosed between 4 years and 6 years [*8*]. It is most likely caused by degenerative changes in the zonular fibres that hold the lens suspended. Indirect evidence suggests that fibrillin may be involved, since it is rich in cystine residues.

Thromboembolic episodes involving both large and small vessels are common [*8,9*]. They have been attributed to enhanced production of thromboxane A_2 [*10*], increased platelet adhesiveness [*8*], endothelial cell damage [*11*], increased prostacyclin synthesis [*12*], activation of factor V [*13*], reduced protein C activity [*14*] and cofactor activity of thrombomodulin [*15*].

Seizure disorders and progressive mental retardation are observed in homocystinuric patients. These findings can be explained partly as a result of repeated strokes caused by thrombotic events of the disease and partly to homocystine neurotoxicity. Homocysteine is a potent neurotoxin, capable of causing neuronal damage because of excessive stimulation of N-methyl, D-aspartate receptors [*4–6*].

The marfanoid features may be explained by fibrillin degeneration due to the increased level of homocysteine. Homocysteine might further interfere with the correct formation of intra- and inter-chain bonds in the early post-translational modification of collagen, and this may partially be responsible for osteoporosis and other skeletal changes.

The biochemical diagnosis of CBS deficiency can be established by measuring blood or plasma methionine [*16*], urinary homocystine and by enzyme assay. In many laboratories elevation of urinary homocystine can be assessed by the nitroprusside test [*17*]. MS/MS analysis of urine provides a more specific method for determining both homocysteine and cysteine-homocysteine. Furthermore, hypermethioninaemia can be detected by MS/MS analysis of blood spots and therefore offers the possibility of neonatal screening for this disorder, as well as other disorders which lead to elevation of methionine. The MS/MS method is also an excellent tool for follow-up of treatment [*7*].

The medical management of homocystinuria includes a methionine-restricted cys-

tine-supplemented diet [*18*] and pyroxidine (vitamin B_6) therapy (200–1000 mg/24 hours) in patients who have the vitamin B_6 responsive disease (40% of affected patients) [*19*]. Folic acid (1–5 mg/24 hours) should be added to the treatment regime [*20*]. Betaine (trimethylglycine) (50–100 mg/kg per day), which serves as a methyl group donor lowering homocystine levels by remethylating homocystine to methionine, should be tried, especially in vitamin B_6 unresponsive patients [*8,21*]. These patients and heterozygous carriers are at increased risk of thromboembolic phenomena and should therefore be kept on prophylactic doses of aspirin [*22,23*].

These therapeutic modalities were tried in all our patients with variable success. Only 4 patients responded to vitamin B_6, resulting in normalization of plasma methionine levels. The other patients may represent the vitamin B_6 unresponsive variety, explaining the failure of vitamin B_6 in their case. Nevertheless, the other medications used played an important role in preventing the more drastic complications of the disease.

References

1. Mudd SH. Biochemical mechanisms in methyl group transfer. In: Fishman WD, ed. *Metabolic conjugation and metabolic hydrolysis.* New York, Academic Press, 1974:297.
2. Streeten BW. Pathology of the lens. In: Albert DM, Jakobiec FA, eds. *Principles and practice of ophthalmology.* Philadelphia, WB Saunders Company, 1994.
3. Byers PB. Disorders of collagen biosynthesis and structure. In: Scriver CR et al., eds. *The metabolic and molecular bases of inherited disease,* 7th ed. New York, MacGraw–Hill, 1995:4029–78.
4. Dunn HG et al. Homocystinuria. A recently discovered cause of mental defect and cerebrovascular thrombosis. *Neurology,* 1966, 16:407–20.
5. Pullan LM et al. Excitatory amino acid receptor potency and subclass specificity of sulfur-containing amino acids. *Journal of neurochemistry,* 1987, 49:1301–7.
6. Kim JP et al. L-homocysteate is a potent neurotoxin on cultured cortical neurons. *Brain research,* 1987, 437:103–10.
7. Rashed MS et al. Diagnosis of inborn errors of metabolism from blood spots by acylcarnitines and amino acids profiling using automated electrospray tandem mass spectrometry. *Pediatric research,* 1995. 38:324–31.
8. Rezvani I, Auerbach V. In: Behrmann RE et al., eds. *Nelson textbook of pediatrics,* 14th ed. New York, WB Saunders Company, 1992:312–4.
9. McCully KS. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. *American journal of pathology,* 1969, 56:111–28.
10. Graeber JE et al. Effect of homocysteine and homocystine on platelet and vascular arachidonic acid metabolism. *Pediatric research,* 1982, 16:490–3.
11. De Groot PG et al. Endothelial cell dysfunction in homocystinuria. *European journal of clinical investigation,* 1983, 13:405–10.
12. Van Maldergem L et al. Increased prostacyclin biosynthesis in a patient

with homocystinuria. *European journal of pediatrics*, 1990, 149:666–7.

13. Rodgers GM, Kane WH. Activation of endogenous factor V by a homocysteine-induced vascular endothelial cell activator. *Journal of clinical investigation*, 1986, 77:1909–16.

14. Rodgers GM, Conn MT. Homocysteine, an atherogenic stimulus, reduces protein C activation by arterial and venous endothelial cells. *Blood*, 1990, 75:895–901.

15. Hayashi T et al. An atherogenic stimulus homocysteine inhibits cofactor activity of thrombomodulin and enhances thrombomodulin expression in human umbilical vein endothelial cells. *Blood*, 1992, 79:2930–6.

16. Bickell H. Neonatal mass screening for inborn errors of metabolism. In: *Recent progress in perinatal medicine and prevention of congenital anomaly* Tokyo, IYC Congress, Ministry of Health and Welfare, Government of Japan, Medical Information Service, 1979:260.

17. Maddocks JL, MacLachlan J. Application of new fluorescent thiol reagent to diagnose of homocystinuria. *Lancet*, 1991, 338:1043–4.

18. *Task Force on Dietary Management of Metabolic Disorders. Report to FDA Contract 2372–2304.* Elk Grove Village, Committee on Nutrition, American Academy of Pediatrics, 1985.

19. Hollowell Jr JG et al. Homocystinuria as affected by pyridoxine, folic acid, and vitamin B_{12}. *Proceedings of the Society for Experimental Biology and Medicine*, 1968, 129:327–33.

20. Wilcken B, Turner B. Homocystinuria. Reduced folate levels during pyridoxine treatment. *Archives of disease in childhood*, 1973, 48:58–62.

21. Smolin LA et al. The use of betaine for the treatment of homocystinuria. *Journal of pediatrics*, 1981, 99:467–72.

22. Al-Essa M et al. *An atlas of common metabolic and genetic diseases.* Riyadh, Saudi Arabia, King Faisal Specialist Hospital and Research Centre, 1997:111.

23. Al-Essa M, Ozand PT. *Manual of metabolic diseases.* Riyadh, Saudi Arabia, King Faisal Specialist Hospital and Research Centre, 1998:107–9.