Homocystinuria (Cystathionine Synthase Deficiency). Results of Treatment in Late-diagnosed Patients

H. Gröbe

Department of Pediatrics, University of Münster, Robert-Koch-Str. 31, D-4400 Münster, Federal Republic of Germany

Abstract. The clinical outcome in 12 late-diagnosed patients with homocystinuria is reported. Three children died: all were mentally damaged and were never treated effectively. Eight children have been treated with pyridoxine—or with a low-methionine diet with supplemental L-cystine—for 2 to 9 years. Follow-up of these patients shows a striking improvement in behaviour and intellectual development in close correlation to the biochemical normalisation. No thromboembolic episodes occurred in adequately treated patients. However, in one child thrombosis of the retinal artery developed during dietary failure. In another patient the characteristic symptoms of an endangiitis obliterans completely disappeared. Both the reversibility and the improvement of some of the main sequelae in homocystinuria emphasize the need to treat all patients, regardless of their age at diagnosis.

Key words: Homocystinuria – Thromboembolism – Pyridoxine – Low-methionine diet – Atherosclerosis.

Introduction

Homocystinuria due to cystathione synthase deficiency leads to a wide spectrum of clinical symptoms. The systems mainly involved are the eye, brain, blood vessels, and skeleton. Thromboembolic episodes are the main cause of death. It is worth emphasizing that the severity of the clinical manifestations varies markedly in affected individuals.

Because all the clinical complications are probably related to biochemical abnormalities arising secondary to the enzyme deficiency, any treatment should control these metabolic sequelae. The two main methods used to achieve biochemical control are (1) administration of pyridoxine in pharmacological amounts; and (2) in pyridoxine non-responders, a methionine-restricted diet with supplementation of L-cystine. The first therapeutic approach is based on the evidence that cystathionine synthase requires pyridoxal phosphate as cofactor. In responsive homocystinuria the cofactor probably stimulates a modification of the mutant enzyme which leads to increased in vivo enzyme activity.

Ideally, treatment should be started in the newborn period before clinical symptoms have developed. However, it is not yet clear if the newborn screening programs carried out to date are sensitive enough to detect all cystathionine-synthase-deficient individuals [22]. Hitherto most of the patients with homocystinuria have been detected when typical symptoms led to diagnostic tests. The clinical outcome is uncertain if treatment is delayed until after clinical abnormalities are manifest.

The purpose of this paper is to report the follow-up of 12 late-diagnosed patients, eight of whom have now been treated for periods of 2 to 9 years.

Patients and Treatment

The diagnosis was established in 11 patients by the demonstration of homocystine and the mixed disulphide of homocysteine and cysteine in plasma and urine, and by increased methionine in plasma. Cystine levels were decreased in plasma—in most of the patients only traces were found. Blood samples were collected in plastic syringes containing heparin; the plasma was immediately deproteinized using sulfosalicylic acid. Amino acid analyses were performed by ion-exchange chromatography using a lithium-buffer system. In an additional child the disorder was diagnosed by the characteristic clinical symptoms, by fulminant thrombosis leading to death, and by the fact that two of this child's siblings suffered from proven homocystinuria.
The main clinical features of the patients are summarized in Table 1. The ages of the patients varied from 8 months to 26 years at the time of diagnosis; thus the disorder was not detected by newborn screening in any case. The symptoms leading to diagnosis were ectopia lentis (5 times), mostly in association with mental retardation and tallness, or mental retardation alone (twice). In 5 patients family studies lead to the diagnosis: 3 showed typical features of the disorder but two were considered to be very mildly affected.

Three children died, all of whom were severely mentally retarded and never effectively treated. In the further 9 patients we began treatment with pyridoxine (up to 900 mg per day) and folic acid, as reported elsewhere [10]. We allowed an unlimited food intake but recommended avoidance of large meals rich in protein. The biochemical response to therapy was monitored by blood amino acid estimations. Five of the nine children were pyridoxine-responsive, as defined if homocystine disappeared from plasma or is only detectable in traces, and when methionine concentration decreased below 1.2 mg/dl plasma. In all the responsive patients we also observed a distinct increase in plasma cystine to normal or near normal values while on treatment (Table 2). Biochemical improvement was evident when the first controls were performed one to two weeks after treatment began, but plasma levels of methionine and homocystine continued to decrease over a period of up to 4 months. Table 2 shows plasma levels of methionine, homocystine and cystine before and after the start of treatment, and the most recent values.

In one child (R.S.) we observed an initial biochemical improvement after pyridoxine administration, but plasma methionine levels subsequently increased and homocystine also appeared (range 0.4–0.6 mg/dl). We thus initiated additional protein-restriction (1.2 g protein/kg body weight per day), and achieved good biochemical control over a 7-year-period.

Results of Treatment

The treatment results are reported with regard to some of the main clinical abnormalities, i.e., (1) the eye, (2) the central nervous system, and (3) the vascular system. Follow-up of growth and platelet-function has been reported elsewhere [11, 12]. We have not differentiated between the pyridoxine responders and non-responders, because in our opinion the symptoms of the disorder are sequelae of the biochemical abnormalities and are independent from the role of pyridoxine.

(1) When the diagnosis was established, seven out of eight patients already suffered from ectopia lentis, an irreversible condition. However, the course of the child in whom treatment with a methionine-restricted and l-cystine supplemented diet was initiated at the age of 14 months is especially noteworthy. Subluxation of the lenses was observed at the age of 3 years but there has been no further deterioration up to the present age of 8 years.

(2) There was a striking and particularly dramatic improvement in behaviour and intellectual development in all the treated patients (Table 3). In no case was further mental regression observed after commencement of treatment. In the seven older patients the most marked changes were due to behaviour disturbances. The improvement began quite abruptly, in correlation to the biochemical normalization and was spontaneous.