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The Natural History of Homocystinura Due to Cystathionine β-Synthase Deficiency

S. HARVEY MUDD,[1] FLEMMING SKOVBY,[1] HARVEY L. LEVY,[2] KAREN D. PETTIGREW,[3] BRIDGET WILCKEN,[4] REED E. PYERITZ,[5] G. ANDRIA,[6] GODFRIED H. J. BOERS,[7] IRVIN L. BROMBERG,[8] ROBERTO CERONE,[9] BRIAN FOWLER,[10] H. GRÖBE,[11] HILDGUND SCHMIDT,[12] AND LESLIE SCHWEITZER[13]

SUMMARY

An international questionnaire survey has been conducted to define better the natural history of homocystinuria due to cystathionine β-synthase deficiency and permit evaluation of treatment. Data were compiled for 629 patients. Among patients not discovered by newborn screening, B_6-responsive individuals on the average have significantly better mental capabilities (mean IQ, 79) than do B_6-nonresponsive individuals (mean IQ, 57). Time-to-event curves are presented for the other major clinical abnormalities produced by this disease. Each occurred at significantly lower rates in untreated B_6-responsive than in untreated B_6-nonresponsive patients, as shown by the following examples: (1) dislocation of optic lenses (at age 10, chances of dislocation: 55% and 82%, respectively); (2) initial clinically detected thromboembolic events (at age 15, chances

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[1] Laboratory of General and Comparative Biochemistry, National Institute of Mental Health, Bldg. 32, Rm. 101, 9000 Rockville Pike, Bethesda, MD 20205.
[2] The Joseph P. Kennedy, Jr. Laboratories of the Neurology Service, Massachusetts General Hospital, and the Department of Neurology, Harvard Medical School, Boston, MA 02114.
[3] Theoretical Statistics and Mathematics Branch, National Institute of Mental Health, Bethesda, MD 20205.
[4] N.S.W. Department of Health, Oliver Latham Laboratory, North Ryde 2113, Sydney, Australia.
[5] Departments of Medicine and Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, MD 21205.
[6] Clinica Pediatrica della II Facolta di Medicina e Chirurgia, Napoli, Italy.
[7] Department of Medicine, University of Nijmegen, Nijmegen, Netherlands.
[8] The Hospital for Sick Children, Toronto, Ontario M5G 1X8, Canada.
[9] Clinica Pediatrica R ⟨⟨G. Gaslini⟩⟩, Universita di Genova, Genova, Italy.
[10] Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Manchester M27 1HA, England.
[11] Kinderklinik der Universität Münster, D-4400 Münster, West Germany.
[12] Kinderklinik der Universität Heidelberg, D-6900 Heidelberg, West Germany.
[13] New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY 10314.

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of having had such an event: 12% and 27%, respectively); (3) radiologic detection of spinal osteoporosis (at age 15, chances of such osteoporosis having been detected: 36% and 64%, respectively); and (4) mortality (at age 30, chances of not surviving: 4% and 23%, respectively). Methionine restriction initiated neonatally prevented mental retardation, retarded the rate of lens dislocation, and may have reduced the incidence of seizures. Pyridoxine treatment of late-detected B_6-responsive patients retarded the rate of occurrence of initial thromboembolic events. Following 586 surgical procedures, 25 postoperative thromboembolic complications occurred, six of which were fatal. Reproductive histories were reported predominately for B_6-responsive patients. Living offspring of either men or women patients had few abnormalities. The evidence is inconclusive whether untreated maternal cystathionine β-synthase deficiency leads to excessive fetal loss. Only 13% of patients detected in screening programs of newborns and classified as to B_6-responsiveness were B_6-responsive, compared to 47% among late-detected patients. Current screening programs that identify neonatal hypermethioninemia may be preferentially failing to detect B_6-responsive patients.

INTRODUCTION

Homocystinuria due to cystathionine β-synthase deficiency is a genetically determined inborn error of the transsulfuration pathway biochemically characterized by increased plasma homocyst(e)ine and methionine and decreased cyst(e)ine. The disease was discovered in 1962, when mentally retarded individuals were screened for abnormal urinary amino acids [1, 2]. Two years later, the enzyme defect, deficient activity of cystathionine β-synthase, was demonstrated [3].* The major clinical manifestations include mental retardation, dislocation of the optic lens (ectopia lentis), skeletal abnormalities, and a tendency to thromboembolic episodes [6].

Once the enzyme defect and the major biochemical aberrations had been defined, dietary therapy based upon methionine restriction and L-cystine supplementation was suggested. This regimen resulted in some degree of control of the biochemical abnormalities, and largely anecdotal evidence emerged that such treatment from the newborn period could prevent or delay clinical manifestations [7–10]. Subsequently, it was found that some patients on normal diets respond biochemically to large doses of vitamin B_6† with decreases in plasma homocyst(e)ine and changes of plasma methionine and cyst(e)ine concentrations toward normal [11], while others do not so respond. Evidence now available strongly indicates that such

* Several other enzyme lesions are now known that also lead to excretion of excess homocystine (homocystinuria) [4, 5]. In this paper, we will deal only with homocystinuria due to cystathionine β-synthase deficiency, and the condition will be designated by the latter name.

† Vitamin B_6 will hereafter be referred to as B_6 or pyridoxine.

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B_6-responsiveness, or lack thereof, is one manifestation of a considerable heterogeneity in the mutations producing deficiencies of cystathionine β-synthase activity [6]. Since 1967, many patients have been given trials or prolonged periods of dietary and/or pyridoxine therapy. These therapeutic trials were carried out in the absence of any randomly selected, untreated control population. More recently, the use of aspirin and dipyridamol has been suggested to prevent thrombosis [12], but neither has been subjected to rigorous testing. Other workers have advocated the administration of betaine to reduce concentrations of homocysteine [13, 14].

Only a few years elapsed between discovery of cystathionine β-synthase deficiency and initiation of various therapies. Consequently, there was little opportunity to accumulate knowledge about the natural history of the condition. It is clear, however, that the age of onset and the severity of clinical manifestations vary widely among affected individuals. Thus, the prevalence and natural history of each of the pleiotropic features remain uncertain. Few data are available upon the impact of maternal cystathionine β-synthase deficiency on reproductive potential and on the fetus. The effects of genetic heterogeneity, as indicated, for example, by B_6-responsiveness or B_6-nonresponsiveness, on each of these manifestations are largely undefined. These gaps in our knowledge impede realistic assessment of the efficacy of various therapies. Since homocystinuria due to cystathionine β-synthase deficiency is a relatively rare disease [6], no single physician or center has accumulated a sufficiently large sample of patients to address these questions. Therefore, we have conducted a worldwide questionnaire survey and collected information in a standardized format on more than 600 patients with homocystinuria due to proven or presumed deficiency of cystathionine β-synthase. Our results, presented in this report, clarify some of the major uncertainties about the natural history of the disease and the role of genetic heterogeneity. They also establish baselines for future evaluation of the effects of treatment in this disease.

METHODS

Data Base

A standardized questionnaire was designed and mailed to each clinician known from a previous study [15] to be caring for patients with cystathionine β-synthase deficiency. Physicians were asked to complete a questionnaire for each such individual about whom they had appropriate information. To encourage participation, the questionnaire was kept relatively simple.* Each patient was identified by first name, first two letters of family name, birth date, and sex. Affected relatives were specified. Further questions focused upon the factor(s) that led to ascertainment, whether the patient was responsive to B_6, and upon the presence and age of appearance of major clinical manifestations. A detailed history of therapy was requested, as well as a reproductive history. To permit use of relevant published material, the respondent was asked to identify articles concerning a given patient. Additional sources of information were identified by a review of the literature and by contacting centers around the world specializing in diagnosis and management of inborn errors of metabolism. Further, physician cooperation was solicited by notices in

* Copies of the questionnaire are available through the National Auxiliary Publications Service (see footnote † to page 10).

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appropriate journals. For some patients upon whom recent information could not be obtained, the study coordinators completed questionnaires chiefly or solely on the basis of published material. Such patients were included only when sufficient details were available to prove that they did not overlap with any patient otherwise included in the study. Data collection occurred during 1982 and early 1983. Data from the completed questionnaires were entered into a computer and verified by proofreading a print-out of the computer data against the original questionnaires. A computer search for duplication due to a single patient having been reported upon by two different physicians detected several such instances, and the redundant information was deleted.

Statistical Analyses

Time-to-event curves were calculated according to the product-limit estimate method of Kaplan and Meier [16]. Comparisons among the curves for statistically significant differences were performed by the procedures of Gehan [17] and Breslow [18]. For evaluation of treatments, numbers of expected events were calculated according to the nonparametric procedures described by Turnbull et al. [19]. Differences between numbers of observed and expected events were tested for statistical significance according to the same procedure.

RESULTS

The Study Population and Criteria for Acceptance into Study

For the present survey, updated information was received concerning 532 homocystinuric patients with proven or presumed cystathionine β-synthase deficiency. To this group was added material on an additional 97 patients obtained primarily from published reports [7, 9, 20–55], bringing the total to 629 patients. All patients admitted to the study had been demonstrated to be excreting homocystine. To restrict the population to cystathionine β-synthase-deficient individuals (thus excluding other causes of homocystine excretion [4–6]), either (1) cystathionine β-synthase deficiency had to have been demonstrated directly by enzyme assay or (2) the patient had to have either hypermethioninemia or dislocated optic lenses. Table 1 shows the similar percent distributions of these findings in patients with and without confirmation of the diagnosis by enzyme assay.

TABLE 1

CRITERIA FOR ACCEPTANCE OF PATIENTS INTO STUDY

	ENZYME ASSAY	
	Performed*	Not performed
Dislocated lens and hypermethioninemia	147 (68.0%)	274 (66.3%)
Dislocated lens only	21 (9.7%)	75 (18.2%)
Hypermethioninemia only	39 (18.1%)	64 (15.5%)
Neither of above	9 (4.2%)	0 (0%)
Total	216 (100%)	413 (100%)

* The following tissues were used for enzyme assays (followed by no. patients, in parentheses): liver (27); both liver and cultured fibroblasts (13); cultured fibroblasts (170); brain (1); phytohemagglutinin-stimulated lymphocytes (3); transformed lymphocytes (1); cultured fibroblasts and phytohemagglutinin-stimulated lymphocytes (1).

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TABLE 2

CLINICAL FEATURES LEADING TO INVESTIGATION FOR HOMOCYSTINURIA

Clinical feature	Sole cause (% of patients)	Contributory cause* (% of patients)	Total in which a cause (% of patients)
Ectopia lentis	20.6	65.0	85.6
Mental retardation	4.0	51.7	55.7
Developmental retardation	1.5	21.0	22.5
Early thromboembolic disorder	1.1	15.0	16.1
Marfanoid characteristics	0.9	36.0	36.9
Bony abnormality	0.2	23.3	23.5
Seizures	0.2	3.0	3.2
Behavioral or psychiatric disorder	0	2.8	2.8
Other†	0.4	10.6	11.0

NOTE: Based on data for 472 patients not ascertained as a result of screening of newborns or screening of all sibs of a proband.

* Includes all patients with the specified feature, as well as at least one other, reported as leading to investigation for homocystinuria.

† Includes a variety of manifestations, none of which was a cause in as many as 2% of the population.

Of the 629 patients, 307 were females and 321 males, close to the expected ratio of 1:1. The sex of one patient was not specified. Sixty-four patients (10.2%) were dead at the time of reporting.

Ascertainment

Data on factors leading to investigation of patients for homocystinuria were available for 618 patients. Of these, 58 were discovered during screening of newborns, and an additional 88 were discovered by screening all siblings after detection of homocystinuria in a proband, leaving 472 patients ascertained on the basis of clinical features. Table 2 displays the frequencies at which each of the major clinical manifestations was the sole reported cause of investigation for homocystinuria or was a contributory cause. Most patients were investigated because of more than one clinical feature, the major exception being the almost 21% initially investigated solely because of ectopia lentis.

B_6-Responsiveness

Of the 629 patients, 231 (36.7%) were classified as biochemically responsive to B_6 when not folate depleted; 231 (36.7%) were classified as nonresponsive to B_6; 67 (10.7%) were judged intermediate in response; and 100 (15.9%) had not been classified. For subsequent analyses in this presentation, neither the "intermediate-response" group, although this may include patients with a biochemically significant response, nor unclassified patients were included in groups designated as "B_6-responsive" or "B_6-nonresponsive."

The relative frequencies of B_6-responsive and B_6-nonresponsive patients among at least two subgroups of the total population differed markedly from the overall frequency. Among the 55 patients who had been both discovered by newborn screening and classified with respect to B_6-responsiveness, seven (12.7%) were B_6-responsive, 43 (78.2%) were nonresponsive, and five (9.1%) were intermediate

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