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The Prognosis of Hyperlysinemia: An Interim Report

J. DANCIS,[1] J. HUTZLER,[1] M. G. AMPOLA,[2] V. E. SHIH,[3]
H. H. VAN GELDEREN,[4] L. T. KIRBY,[5] AND N. C. WOODY[6]

SUMMARY

Ten patients with familial hyperlysinemia with lysine-ketoglutarate reductase deficiency, identified through newborn screening programs or family surveys, were selected for review. Ages ranged from 2 to 24 years when last examined. A low-protein diet had been administered to two patients, which reduced the plasma lysine levels from 20 mg per dl or more to about 12 mg per dl. The rest were untreated. Mental development was judged normal or above average in nine. Mildly subnormal performance in three was considered appropriate to family and social background. No adverse mental or physical effects could be attributed to the hyperlysinemia. A normal child has been born to a mother with hyperlysinemia, indicating that the fetus may develop normally despite exposure to high lysine levels.

INTRODUCTION

Early reports of the association of hyperlysinemia, neurological damage, and mental retardation led to the reasonable presumption that increased levels of lysine and/or its metabolites might be harmful [1, 2]. More recent, well-documented case reports of hyperlysinemia without neurological impairment made it clear that the relation was not constant [3, 4]. However, the possibility remained that hyperlysinemia was damaging in some cases and that reduction of lysine intake should be imposed. Effective dietary control is difficult because the abundance

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[1] Department of Pediatrics, NYU School of Medicine, 550 First Avenue, New York, NY 10016.

[2] Department of Pediatrics, Tufts University School of Medicine, Boston, MA 02111.

[3] Neurology and Pediatrics Service, Massachusetts General Hospital, Boston, MA 02114.

[4] Department of Pediatrics, University Hospital, Leiden, The Netherlands.

[5] Department of Pathology, University of British Columbia, Faculty of Medicine, Vancouver, British Columbia, Canada.

[6] Department of Pediatrics, Tulane University School of Medicine, New Orleans, LA 70112.

of lysine in natural diets makes it necessary to use synthetic diets if the objective is to reduce plasma lysine to normal levels.

The identification of a discrete genetic disease in which the plasma lysine level regularly exceeds 10 mg per dl and commonly approximates 20 mg per dl has made it possible to approach the question of deleterious effects of hyperlysinemia more definitively [5]. The hyperlysinemia is caused by a deficiency in lysine-ketoglutarate reductase and saccharopine dehydrogenase, the enzymes that effect the first two degradative steps in the lysine pathway [6].

This report is limited to patients in whom a specific diagnosis of lysine-ketoglutarate reductase deficiency has been made. Cases have been selected in which the original diagnosis was made in a newborn screening program or as the result of family surveys of affected patients. One family was discovered during an investigation of short stature [4]. Cases were rejected if the diagnosis was made during the investigation of a presenting complaint of neurological or intellectual impairment. Ten cases have met the criteria and are included in this report.

METHODS

Lysinuria and hyperlysinemia were demonstrated with conventional methods. Lysine-ketoglutarate reductase was measured in skin fibroblasts grown in tissue culture. Fibroblasts were disrupted by freezing and then incubated with radioactive lysine, NADPH, and α-ketoglutarate. Radioactive saccharopine was isolated by high-voltage electrophoresis and column chromatography [5]. Minor modifications in the technique were made in the enzyme assays on patient 9 [4].

CASE REPORTS

Cases 1 and 2

Subject A. Ja and J. Ja were diagnosed as having familial hyperlysinemia in a survey of the family of a mentally retarded child with the metabolic anomaly [3]. Subject A. Ja was last seen at age 10 when both her physical and mental performance were considered above average. Subject J. Ja at age 12 had a mental age of approximately 8 years. He was noted to resemble his father, physically and mentally. The family lives in an isolated rural community in which there is frequent intermarriage.

Case 3

Subject K. Gu is first cousin to the above children [3]. At age 13, she was extremely obese because of excessive eating, similar to her father. Her IQ was 100.

Case 4

Subject P. Gi was diagnosed in a screening program at age 2 months when the serum lysine was 26 mg per dl. He was placed on a low-protein diet, which reduced the lysine level to about 12 mg per dl. At age 4½, he appeared normal and in good health.

Case 5

Subject A. Ro was detected in a newborn screening program. Plasma lysine was 20 mg per dl. A low-protein diet was instituted, which has maintained the plasma lysine at 11–14 mg per dl. At age 10, his IQ was 117 and he was advanced in school performance. At age 13, he was short (as are his parents) but otherwise normal.

Case 6

The diagnosis of hyperlysinemia was made at age 15 days in subject S. Ha. He developed febrile convulsions at age 7 months. Active rickets was diagnosed and successfully treated. At age 3½, he was considered normal. The details of this case have been separately reported [7].

Cases 7 and 8

Lysinuria was detected in subject S. Be as part of a newborn screening program. Subject J. Be is her older brother, identified during family survey. Subject S. Be was age 2 and subject J. Be was age 5 when last seen. Both appeared normal.*

Cases 9 and 10

Lysinuria and hyperlysinemia were detected in a 7-year-old boy during investigation of short stature. His IQ was 88. He came from a family of low social class among whom many members had been slow learners. His sister was also small and had hyperlysinemia. Small stature, without hyperlysinemia, was frequent in the maternal family [4]. When last seen at age 17, the boy appeared normal. He worked as an unskilled laborer. The sister is 24 years old, married, and has had a normal baby. She has had several jobs requiring no special skills. In both patients, the hyperlysinemia has persisted unchanged.

RESULTS

Of the 14 patients diagnosed in the laboratory of the senior author as having lysine-ketoglutarate reductase deficiency, nine met the clinical criteria and eight patients in five families are included in this report. Four had been detected in newborn screening programs and four in family surveys of a previously diagnosed case. An additional family with two affected siblings was found during the investigation of a 7-year-old for short stature [4]. The results of the enzyme assays have been reported [4, 5, 8] except for those in cases 7 and 8 (see CASE REPORTS). The fibroblasts of these patients were also assayed in our laboratory with results typical of lysine-ketoglutarate reductase deficiency.

The ages when the patients were last seen by their physicians ranged from 2 to 24 years. In no instance has there been progression of disease or has any individual required institutionalization. Two of the older children were reported as intellectually advanced (cases 2 and 5). Neurological defects were conspicuously absent. One subject had dislocated lenses (case 2), and two were of short stature (cases 9 and 10). The short stature proved to be an independent familial trait [4].

Low-protein diets were prescribed in infancy for two patients, and have been maintained throughout life (cases 4 and 5). Protein intake was reduced to the level required for growth. Plasma lysine concentrations fell from approximately 20 mg per dl to about 12 mg per dl in both cases. Both patients have done well.

DISCUSSION

The investigation of obscure cases of mental retardation and neurological damage commonly includes a study of amino acid metabolism. When abnormalities are

* We are indebted to Dr. R. M. Nakamura for a recent report on cases 7 and 8.

uncovered, their relation to the presenting complaint is uncertain. One approach to ascertaining the relation is to review the experience with cases detected through screening programs and family surveys. That is the approach that we have used in the present study and which has been used previously for histidinemia [9].

The results in the present series of 10 patients with hyperlysinemia are reasonably clear. An adverse effect could not be attributed to hyperlysinemia in any of the cases. The early devastating effects of some hyperaminoacidurias are not seen in hyperlysinemia. Patients with hyperlysinemia generally achieve normal intellectual performance and may even perform above normal. It is not yet possible to exclude delayed, subtle, or rare adverse effects of hyperlysinemia.

A particularly stringent test of the potential pathogenicity of hyperlysinemia was provided by the pregnancy of case 10. In contrast to the devastating effects of maternal phenylketonuria, a normal child was born to a mother with hyperlysinemia. Although serum lysine levels were not measured at birth, it is a reasonable presumption that the intrauterine fetal lysine levels were at least as high as the maternal levels. Under normal conditions, a gradient of lysine is maintained toward the fetus [10] and transfer rates of lysine across the placenta are about the same as for phenylalanine [11].

From the currently available data, the strenuous efforts required to reduce plasma lysine concentrations to normal are not indicated. To accomplish such reductions, it is necessary to lower protein intake to levels providing minimal lysine requirements and to supplement the diet with purified amino acids in amounts sufficient to satisfy the remaining nitrogenous requirements [12]. The psychiatric and physical risks and the expense outweigh any potential advantage. A similar firm position cannot be taken with the administration of low-protein diets, although there is no evidence supporting their use. The present observations do not permit the unequivocal statement that hyperlysinemia is entirely benign.

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THE HUMAN GENE MAPPING WORKSHOP VII will be held on the UCLA campus, August 21–26, 1983. Active workers in gene mapping should write for information to: Robert S. Sparkes, M.D., Division of Medical Genetics, Department of Medicine, UCLA Center for the Health Sciences, Los Angeles, CA 90024.

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