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A Case of Hartnup Disorder with Hypoalbuminemia and Edema*

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Hartnup disease is an autosomal recessively inherited disorder, characterized by gross aminoaciduria involving all neutral amino acids except glycine, proline, and hydroxyproline. The basic metabolic defect in Hartnup disease results from the genetically induced defect in both the intestinal and renal transport of neutral amino acids.[1-2]

The clinical manifestations may include mental retardation, psychotic behavior, cerebellar ataxia, and pellagra-like rashes.[3, 4]

Although a biochemical disorder is always present, the clinical manifestations of Hartnup disease are intermittent and variable. Some of the recently described asympthomatic cases have been recognized only through routine screening.[5, 6, 7]

This report describes a five year old girl with Hartnup disease presenting with hypoproteinemia and edema, but free of other clinical findings.

Case Report

M.K., a 5 year old girl, was admitted to Hacettepe Children's Hospital on Oct. 8, 1975. The mother's pregnancy and delivery were normal. The child had been healthy until 3 to 4 months prior to admission. At that time her feet, legs, and hands became edematous. The parents were first cousins and appeared healthy. Their first child had died at 2 years of age from an unknown illness.

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Physical examination revealed her weight to be 15 kg, (below 3 percentile), height 98 cm, and head circumference was 54 cm. Her mental age corresponded with her chronological age. Except for severe edema on both feet, legs, hands, and forearms, there were no other abnormalities.

Laboratory findings were as follows: Hemoglobin 10 g/dl, hematocrit 38 1/1, RBC 12.2×10^9/1 and erythrocyte morphology was normochromic normocytic. Routine urine analysis was normal with a specific gravity of 1.022. Total serum protein was 4.8 g/dl (albumin 2.5 g/dl, globulin 2.9 g/dl). SGOT 21 U, SGPT 22 U, creatinine clearance 12 ml/min, and blood electrolytes, IVP, and EEG findings were normal.

Two dimensional paper chromatography[8] of urine using Butanol acetic acid, water (12:3:5) as the basic solvent and phenol, ammonia, water (120:1:60) as a second solvent, showed the characteristic pattern of Hartnup disease (Figure 1).

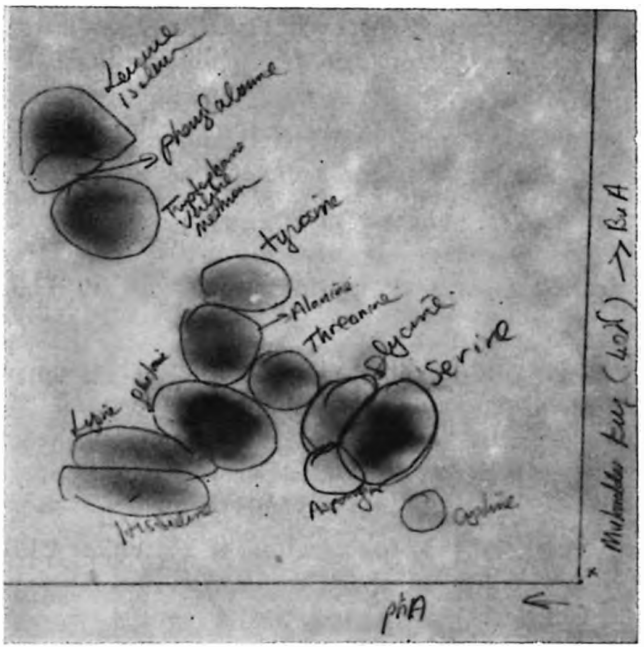

Figure 1
Chromatographic studies of urinary amino acids with the typical "Hartnup" pattern.

Tryptophan Loading Test: 100 mg of L-Tryptophan per kg body weight was administered orally to the patient as well as the normal control who was approximately the same age. Serum tryptophan levels were determined at the beginning and at hourly intervals for the next

four hours. In the patient the baseline serum tryptophan level was slightly lower than the control, and even after loading, the maximum level was not higher than 1 mg tryptophan/dl. In the control, the serum tryptophan level reached 10 to 11 mg/dl in the first and second hours of the tests (Figure 2).

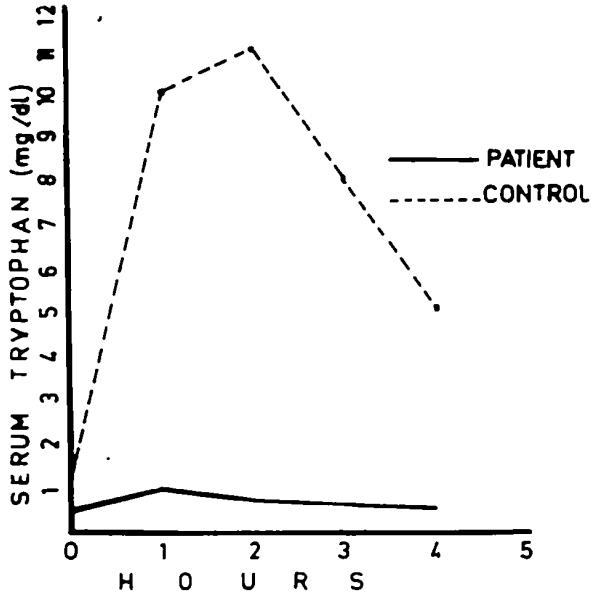

Figure 2
Serum concentrations of tryptophan after oral loads of L-tryptophan (100 mg/kg body weight in patient and in control).

The effect of ingestion of L-tryptophan on the urinary excreation of tryptophan, kynurenine, indican, and indolylacetic acid were also investigated during 24 hours using two dimensional paper chromatography stained with Ehrlich' reagent.[9] All urine samples from the patient produced tryptophan spots larger than those of the control. There were medium IAA (indolylacetic acid) and kynurenine spots in the 2 hour urine sample from the control, but not from the patient. Larger spots of indoexyl sulfate and indolylacetyl-L-glutamine were observed in the patient's urine at 6, 10, and 18 hours after loading, but were not seen in the control.

Discussion

The typical neutral aminoaciduria and the defect of absorbtion of L-tryptophan after loading the patient leaves no doubt that this was a

case of Hartnup disease. Increased urinary excretion of indoxysulfate and indolyacetyl-L-glutamine which was observed after 6 hours of tryptophan loading are also indications of abnormal tryptophan absorption.

In spite of the pathognomotic laboratory findings, the patient's history and physical examination did not specifically suggest Hartnup disease.

Neurological findings such as unsteadiness of gait, clumsiness, nystagmus, and tremor which are the characteristics of cerrebellar ataxia or emotional instability, had not been observed until the patient was 5 years old. Mentally she was normal. Although she was from one of the sunny villages near Ankara, and usually played outside the house, she did not experience the severe skin changes of the disease which resemble dietary pellagra. On the admission, however, there was a slight dryness and eczematoid lesions on both her thighs. Because routine urinary examination and IVP were normal, and on the basis of severe growth retardation and edema of feet, legs and hands, hypoproteinemia and hypoalbuminemia, the patient was originally diagnosed as having protein-calorie-malnutrition. However, when urinary amino acids were investigated by chance, it was discovered that this was one of the unusual Hartnup cases. Firstly typical clinical findings had not been observed and secondly, growth retardation and edema with hypoalbuminemia were prominent features of the patient.

In approximately 43 presented cases,[4] growth retardation has usually been observed, but we found only one reported case with hypoalbumunemia and edema.[10] However, that case was different from our case in that the other typical clinical findings of Hartnup disease were also present.

The dietary history of our patient indicated that her daily protein intake was near the lower limits of normal. Certainly the defect of the absorption and reabsorptions of several amino acids were not componsated with such a limited protein intake and as a result hypoalbuminemia and edema developed.

The cilinical manifestations of Hartnup's disease, namely ataxia, mental and behavior changes, and pellagralike skin lesions, are attributed to niacin deficiency due to the abnormality of the absorption of L-tryptophan.[4] It is interesting that the patient did not show any clear signs of niacin deficiency in spite of hypoproteinemia and hypoalbuminemia. If her daily meals had contained more protein she probably would not have developed edema and would not have been refered to the hospital.

Failure to thrive has been one of the indications for systematic screening for some inborn errors of metabolic diseases.[11] This case shows that, besides growth failure, children with hypoalbuminemia and edema who do not have any other disease to account for these findings should also be investigated for metabolic disorders in particular, for Hartnup disease.

Summary

A patient with Hartnup disease is presented. It was discovered that this was one of the unusual Hartnup cases. Firstly the typical clinical findings had not been observed. Secondly growth retardation and edema with hypoalbuminemia were prominent features of the patient.

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