CLINICAL CONFERENCE

Cystinosis

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DR. KRETCHMER: For many years pediatricians have known a group of inherited diseases associated with specific biochemical defects. Actually, these diseases were first compiled and demonstrated by Sir Archibald Garrod approximately 50 years ago. The case we would like to present, one of cystinosis or cystine storage disease, is an example of one of the so-called inborn errors of metabolism.

Patient B.F. was admitted to the New York Hospital with a chief complaint of growth retardation. She was the product of a normal, full-term, spontaneous delivery, and developed well until 2 years of age when growth retardation was noted.

The child has photophobia and has always demonstrated polyuria. There has been no history of convulsions. The patient has been followed by a private physician for the past 2 years.

The members of the family are indicated in Figure 1. There were three deaths, the maternal father who died of diabetes mellitus complicated with arteriosclerosis; and two siblings of the father, one who died of poliomyelitis and the other of pneumonia.

The father and mother of the present patient are living and well, one sibling died last year at the age of 7 years of cystine storage disease, and an elder male sibling of 11 years is alive and well.

The physical examination indicated a temperature of 37.7°C, a pulse of 100, respirations of 20, and a normal blood pressure. The patient is 92 cm tall and weighs 13.2 kg, and is a small, doll-like, pale, co-operative, bright girl. Also noted were the diminutive stature, haziness of the corneas, photophobia and polyuria. The neurologic examination was physiologic in all respects.

Laboratory examinations were as follows.

Urine: Specific gravity 1.010 and pH 6.0; protein excretion, 0.7 gm/12 hr (the normal figure for this laboratory is less than 0.1 gm/12 hr); in a 12-hour specimen, erythrocytes 0; leukocytes 2,200,000 (normal for a female of this age), casts 50,000 (25,000 is normal in this laboratory); the child also had glycosuria and the sugar was identified as glucose.

Chemical analyses of the blood: Urea-nitrogen 30 to 45 mg/100 ml; carbon dioxide 22 mM/l; sodium 138 mEq/l; potassium 2.7 to 3.5 mEq/l; albumin 5.0 and globulin 2.5 gm/100 ml; cholesterol 375 mg/100 ml; creatinine 1.8 mg/100 ml (approximately twice normal); alkaline phosphatase 4.1 units (normal); calcium 4.8 mEq/l; and phosphorus 3.2 mEq/l. The urea clearance was 20% of normal for adults. The clearance of inulin was 12% of normal for adults and the clearance of amino-nitrogen was 4 ml/min (normal clearance is 1 to 2 ml/min). As the glomerular filtration rate is one-fifth of the normal, the amino-nitrogen was cleared at approximately 20 to 30 times the normal rate.

Amino-nitrogen in the blood was 4 mg/100 ml (in our series the mean normal is 2.5 mg). It is interesting that in at least 12 different determinations the concentration of amino-nitrogen in the urine ranged from 2 to 19 mg/kg/24 hr with an average of 11 mg/kg/24 hr (normal, 2 to 4 mg/kg/24 hr).

By paper chromatography of the urine a generalized increase in amino acids, except for cystine, was demonstrated. In tryptophan load tests, no xanthurenic acid was formed. Four per cent of a tyrosine load was excreted, which is normal. Considering the clearance of inulin, this child is clearing tyrosine about 5 to 10 times above normal.

Together with Dr. Leon Hellman of the Sloan-Kettering Institute, turnover of plasma protein was measured using C-14, and the half-life was found to be 15 days which is approximately normal.

Intracellular deposition of crystals resem-

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bling cystine was found in the bone marrow. Crystalline deposits were seen in the cornea by slit lamp.

(The patient, 4 9/12 years of age, was presented.)

The major demonstrable physical feature was the diminutive stature.

QUESTION: Can one see the crystals in the cornea without a slit lamp?

DR. KRETCHMER: Actually the crystals can be seen if the eyes are viewed laterally with an ophthalmoscope. A slit lamp is not required for this preliminary examination.

The roentgenograms of the bones of this child were negative. Should we see them?

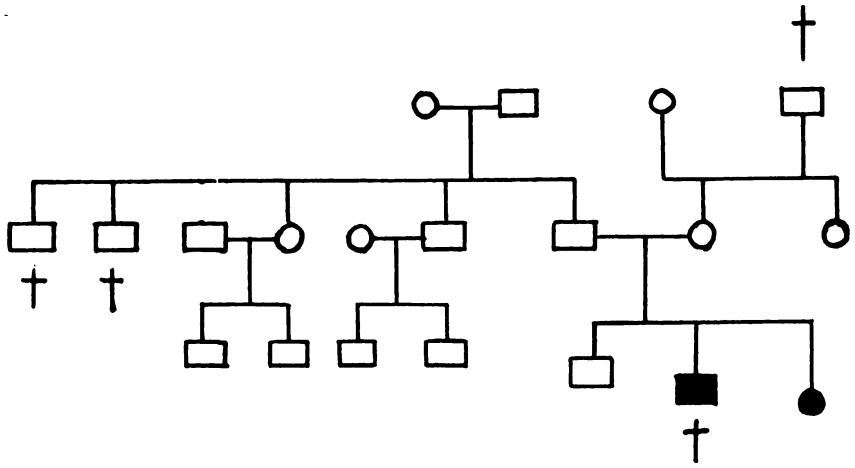

FIG. 1. Family of patient B.F.

= cystine storage disease.

= death.

DR. LEVINE: Do they show anything, Dr. Baker?

DR. BAKER: Very minimal osteoporosis. Later on they will probably show the usual rachitic changes found in these patients. The roentgenograms are normal now.

DR. LEVINE: What are these "usual" rachitic changes?

DR. BAKER: Typical rickets—swollen, cupped metaphyses and a generalized loss of calcium from the tubular bones.

DR. KRETCHMER: We have presented a little girl who has a pronounced, inherited, biochemical defect, the pathogenesis of which is unknown. Probably, a better understanding of this disease can be obtained if we discuss the mechanisms operating at the cellular level.

The gene or hereditary unit, is located on a chromosome within the nucleus. This gene can act with or without other genes to produce a protein which may be an enzyme and therefore act as a catalyst.

In order for the gene to produce a protein such as an enzyme, other factors should be considered. Precursor substances must be present and whether these precursor substances are amino acids or peptides is not known. Extraneous factors such as hormones, nutrition, or poisons may influence the formation of the enzyme; either to increase or to decrease the concentration or activity.

The enzyme or protein resulting from action of the gene can either function in the intracellular environment or may be dispersed in the blood stream in a form such as hemoglobin, or any of the various proteins known to be in the blood. These proteins are all related to and are derived from action of the genes.

Normally, the enzyme would act on a substance A (substrate) to convert it to a new substance B (product). The resultant substance B can be metabolically important or it may be merely an inactive end product, an excretory product of metabolism. Now, one can postulate a situation wherein the gene does not act to produce the enzyme or where various environmental factors prevent the production of the enzyme. Thus, minimal amounts of product B result from A, and large amounts of A accumulate because a partial block exists. Substance A may be toxic to the individual as

it accumulates, or new excretory products may form from A.

The development of the enzyme is important in this mechanism, and we and others have actually shown that enzymes do develop as the individual matures. In the premature infant, during the initial stages of formation of the enzyme p-hydroxyphenylpyruvate oxidase, substance A or p-hydroxyphenylpyruvate accumulates and is excreted in the urine.

In Figure 2 a few disorders associated with incomplete metabolism of amino acids are indicated. A similar chart could be constructed for the metabolism of lipids or carbohydrates. An amino acid can follow a variety of pathways to form final end products. The ultimate

Cystinosis, according to the prevalent concept, results from a block in the most important type of metabolism of amino acids, the incorporation of an amino acid into a protein. Cystinuria results from a block in the specific transfer of such amino acids as cystine, lysine, and arginine. On the other hand, there is a block in the generalized transfer of all amino acids in hepatolenticular degeneration, or Wilson's disease. In this disease excretion of all of the amino acids is increased in the urine.

The problem with which we are concerned today is cystinosis. It is presumed from the data which have so far been collected that the primary block in metabolism is a block in protein synthesis. Therefore, a group of definitive

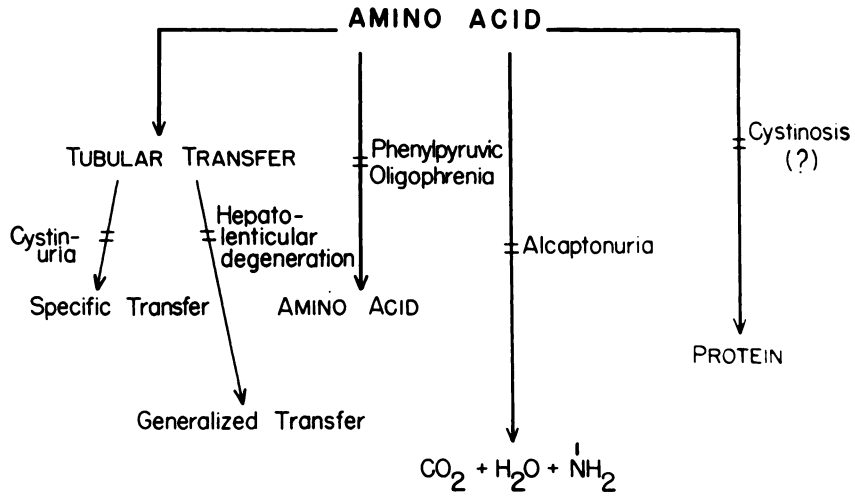

FIG. 2. Some disorders associated with incomplete metabolism of amino acids.

end products for an amino acid are carbon dioxide, water and free amino groups; the latter may be excreted in the form of urea.

Another well-known metabolic pathway of amino acids is synthesis into protein. A third pathway for amino acids such as the essential amino acids, is conversion to other amino acids. Finally, in the total economy of the organism, the amino acids are reabsorbed from the glomerular filtrate back into the total organism via the renal tubule.

Depending on the genes affected, we can expect different disorders to occur in the various pathways. An example of a deficiency in the conversion of one amino acid to another exists in phenylpyruvic oligophrenia. A deficiency in the complete catabolism of an amino acid is prominent in alkaptonuria.

clinical manifestations and chemical findings are encountered in this child: There are cystine deposits in the reticuloendothelial system and in the cornea. These are associated with renal insufficiency, hyperphosphaturia, hypokalemia and a variety of other characteristics which are either directly due to the disease or result from the malignant character of the disease.

The problem of the terminology in this disease has concerned many people; the disease has been known as the Fanconi syndrome, the Lignac-Fanconi syndrome, the Debré-DeToni-Fanconi syndrome. Probably the most correct name, which is ignored, is the Abderhalden-Kaufman-Lignac syndrome.

In cystine storage disease, it is not known whether the cystine deposits are actually the result of the group of clinical findings or

whether cystine deposition produces the manifestations. Cystine is well known to be one of the most insoluble of the amino acids and, therefore, it would have a tendency to precipitate when present in high concentration.

There are many workers who believe that this disease is primarily a renal disease. This conclusion is somewhat supported by the work of Darmady. He showed that these children have a constriction of the neck of the proximal tubule. However, the physiologic importance of this morphologic finding is vague.

The prognosis is poor for this child, and the usual cause of death in these children is renal insufficiency, of which rather severe physiologic evidence is present.

Present therapy in these disorders consists of removal of the offending substrate. The eventual treatment of these disorders of incomplete metabolism must, in general, be derived from discovery of an alternate metabolic pathway so that substances which accumulate can be handled by other enzymes. As predicted by Dr. Pauling of the California Institute of Technology, treatment could also be accomplished by the replacement of the absent or defective enzyme or by inducing the individual to develop the enzyme normally.

QUESTION: Is the concentration of cholesterol usually elevated in the blood in this condition?

DR. KRETCHMER: It has been reported to be elevated in this condition.

QUESTION: Is there any special significance to that?

DR. KRETCHMER: So far no one has attached any particular significance to the hypercholesterolemia, but it has been found in at least 50% of these patients.

QUESTION: What is meant by turnover of protein?

DR. KRETCHMER: The turnover of protein in the plasma is an approximation referring to the average rate of the anabolism and catabolism of plasma proteins. This rate is usually given as the time required for half of the proteins to be built up and broken down.

The proteins in this child are "turning over" within 15 days. We thought that this might give information as to whether there was an anabolic or catabolic defect in cystine storage disease.

QUESTION: At necropsy do these children show nephrocalcinosis?

DR. KRETCHMER: This is a completely different disease from Lightwood's syndrome. These patients do not show nephrocalcinosis. In fact, very often at necropsy of children who die early, the kidneys are completely normal; deposition of stones or calcium is not seen as one would in idiopathic renal acidosis.

QUESTION: What is the mechanism of the glycosuria?

DR. KRETCHMER: That is a very difficult question. The exact mechanism for glucose transport is unknown. It has been presumed through the years that glucose is transported through the aegis of phosphorylation, i.e., phosphate is bound to a glucose, and the glucose then is able to enter the cell. This theory is slowly gaining disrepute. The question of the mechanism of the glycosuria can only be answered indefinitely by indicating that there is undoubtedly a defect in the transport of glucose in the renal tubule.

QUESTION: How are you treating this child?

DR. KRETCHMER: We are treating this child primarily with potassium for the hypokalemia, and also with vitamins. This patient, in contrast to other children with cystine storage disease, does not have the usual acidosis. Therefore, we do not have to use alkalinizing solutions. She also does not have excessive phosphaturia, so that phosphate does not have to be replaced.

DR. LEVINE: Do you want to say anything about the death of her brother?

DR. KRETCHMER: The sibling of the patient died of severe renal insufficiency and hypertension with congestive heart failure. At necropsy his kidneys were small; histologically they showed hyalinized glomeruli and no crystals were present. The kidneys did not have the appearance of glomerulonephritis. Crystals were found in the spleen, lymph nodes, bone marrow and Kupfer cells. Dr. Jean Oliver is dissecting the tubules in order to visualize any constriction in the neck of the proximal loop.

QUESTION: We have seen a family in which one child died very early, and a second died within the first week of life, and a third developed a picture like the patient presented here. There are two boys in this family, both of whom are entirely normal. The three who died were girls.

DR. KRETCHMER: There is no indication of sex linkage. This condition is apparently in-

herited through a recessive autosomal gene, in contrast to the Fanconi syndrome in the adult, where inheritance is probably through a dominant gene. There is no indication of sex linkage, so far as I know. In the present family a boy and a girl were afflicted.

QUESTION: Is it possible to prepare a diet deficient in cystine, and would such a diet be compatible with life?

DR. KRETCHMER: That is a question that comes up quite often, especially in view of the results obtained with a diet low in phenylalanine in phenylpyruvic oligophrenia. In answer to the question, I think that a diet low in cystine would not be completely compatible with life and growth. In addition, cysteine, homocystine and methionine would have to be removed from the diet of these children; at least one of these must be available to permit life and protein synthesis. One would have to presume that cystine is the basic cause of all the difficulty, if treatment with a diet low in cystine was to be justified.

QUESTION: Is there any relationship between cystinosis and cystinuria, genetically?

DR. KRETCHMER: No. Cystinuria also results from the action of a recessive gene, and that is the reason it is included in Figure 2. Cystinuria is a disease of amino acid transfer in the renal tubules involving the transport of cystine, lysine, arginine, and ornithine. However, there is no genetic relationship between cystinuria and cystine storage disease.

QUESTION: Do these youngsters have a peculiar odor to their bodies?

DR. KRETCHMER: No. These patients do not have a peculiar odor, such as the musty odor observed in children with phenylpyruvic oligophrenia.

QUESTION: What is the longest survival?

DR. KRETCHMER: The most recent report was a compilation of 14 cases by Bickel, and the oldest child included was 10 years. The little boy, sibling of the present patient, was just past his seventh birthday.

QUESTION: The reason I asked the question is because of a boy of about 12 years who was considered to be a diabetic, and at necropsy we found a cystine-appearing material in the tubules of the kidneys and decalcification of the bones. We wondered whether this was an extremely rare example of cystinosis.

This boy was not small for his age, but I was told that this was a characteristic case of DeToni-Fanconi's disease.

DR. KRETCHMER: The terminology has created much confusion and apparently there was considerable discussion of it at the recent International Congress of Pediatrics. Cystine storage disease should be designated the Abderhalden-Kaufman-Lignac syndrome. The Debré-DeToni-Fanconi syndrome is different; the prominent signs are glucosuria, aminoaciduria and rickets, but there are no deposits of cystine crystals.

DR. LEVINE: Thus these are two different conditions which may or may not be related, but they certainly present different clinical pictures.

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