CYSTINOSIS

A Clinical Report of Three Cases in One Family

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ALTHOUGH cystinosis or cystine storage disease has generally been considered to be a somewhat rare condition, recent medical literature would indicate that the disorder is probably much more common than has previously been appreciated. Ever since the first case of cystine storage disease was described by Abderhalden in 1903 there has been a gradual accumulation of well documented cases of the disorder in the literature. By 1952 56 proved cases of cystinosis had been reported: 53 in the European literature and 3 from the United States. Since that time a few additional cases have been published in the American literature, with the latest two cases incorporated in an excellent critical review on the disorder by Worthen and Good.

It is not surprising that in recent years there has been an increasing frequency in the diagnosis of cystinosis. In earlier times the diagnosis of cystinosis or cystine storage disease was generally made after death with the identification of deposits of cystine crystals in the reticuloendothelial system and kidneys. Esser in 1941 was probably the first author to call attention to a finding of great diagnostic importance whereby the diagnosis of cystinosis could be established in vivo with the demonstration of cystine crystals in aspirated bone marrow. About the same time Bürki reported that deposits of cystine crystals could be identified in the cornea and conjunctiva by slit-lamp illumination. The demonstration of characteristic cystine crystals in biopsied lymph nodes is another diagnostic procedure which definitely establishes the diagnosis of cystinosis in vivo. There is no question, however, that despite these aids to the ante-mortem diagnosis of cystine storage disease the presence of cystine crystals may still be overlooked. Thus, although there has been an increasing number of reported children with cystinosis the true incidence of the disease is yet to be determined.

It is the purpose of this report to present three cases of cystinosis occurring in one family, all three diagnosed in vivo by the demonstration of typical cystine crystals in aspirated bone marrow.

CASE REPORTS

Case 1

D.M.T., a 28-month-old white female, was admitted to the pediatric service of the Jefferson Medical College Hospital on December 15, 1953 with the chief complaints of vomiting, irritability and "heavy breathing" of 48 hours duration.

The child was in her usual state of health until 2 days before admission when she suddenly became listless, anorectic and wished to be carried about. She was afebrile and had no signs of an upper respiratory infection. In the next 24 hours there was no change in the child's condition although it was noted that she exhibited a marked thirst and that her breathing was somewhat labored. She was seen by a local physician on the day before admission who advised an increased fluid intake and prescribed antibiotics. Her condition did not improve and during the ensuing day she became more listless, vomited on several occasions and showed a progressive increase in thirst. The parents detected a "sour odor" on her breath and felt that respirations were more labored than previously noted. On the day of admission the child was obviously confused, disoriented and appeared to have lost considerable weight.

PAST HISTORY: The patient was the result

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of a full-term, uncomplicated pregnancy and delivery. The birth weight was stated to be 3.2 kg. Although her motor development and intelligence were thought to be normal, her weight gain was far from satisfactory. She gained well until 8 months of age at which time she weighed approximately 9.0 kg. From 8 months of age until the present time the child's appetite was described as capricious with many episodes of non-projectile vomiting shortly after meals. There was a tendency to repeated bouts of constipation and an obvious thirst that seemed excessive. The parents explained the capricious appetite and episodes of emesis on the basis of "a feeding problem" and repeated "allergy" to certain foods. Despite the good initial weight gain for the first 8 months of life the child weighed only 7.7 kg at 1 year of age and was said to weigh 9.3 kg prior to the onset of the current illness.

The patient had been hospitalized at another teaching institution in the city for a period of 14 days in September, 1952. Her complaints at that time were those of diarrhea-like stools and an ill-defined skin rash. A tentative diagnosis of celiac disease was made and the infant treated accordingly. After no apparent improvement in the child's condition the parents arranged for the infant's release against medical advice. At home she was treated with a soya bean formula (Mullsoy®) and protein hydrolysates (Nutramigen®) with gradual improvement in the skin rash and the character of the stools. During the 4 months prior to the onset of the current illness she was tolerating a normal diet and appeared quite well except for the failure to gain weight.

**Family History:** The mother and father were in good health and were 24 and 25 years of age, respectively. The marriage was not consanguineous. Although there was no family history of diabetes, renal disease, etc., there was an alleged allergic background on both sides, viz. allergy to milk and hay fever. A 14-month-old male sibling was said to be in good health except for a history of frequent colds and sore throats.

**Physical Findings:** On admission to the hospital on December 15, 1953 the child's temperature was 37°C, pulse 130/min and respirations 58/min. Examination revealed a desperately ill, frail, 28-month-old white female child with marked respiratory distress. The weight was 8.2 kg and body length 75 cm. The skin was dry and showed obvious loss of turgor and elasticity. The eyeballs were sunken; tongue and mucous membranes quite dry, and the lips pale, dry and cracked. Her breath was definitely acidic in character. Respirations were rapid and deep with marked flaring of the alae nasi. The anterior fontanel was closed and there was no obvious bossing of the skull. Examination of the lungs and heart was not remarkable. There was a suggestion of a rachitic rosary. The liver was palpable 3 cm below the costal margin but no splenic enlargement was detected. There was no lymphadenopathy and examination of the extremities as well as a gross neurologic evaluation were said to be within normal limits.

**Laboratory Findings:** The laboratory studies were as follows: complete blood count revealed a mild anemia of 8.5 gm/100 ml, a total leukocyte count of 12,700/mm³ and a relatively normal differential count. The urinalysis showed no trace of sugar but was strongly positive for acetone. The initial blood chemistry studies revealed the carbon dioxide combining power to be 9 meq/l, chloride 109 meq/l, and potassium 3.6 meq/l.

**Therapy and Course:** The patient was treated with fluids intravenously which contained lactate, glucose in water and minimal amounts of potassium, with little, if any, clinical improvement. Repeat blood chemistries several hours after admission revealed the carbon dioxide combining power to be 10 meq/l, chloride 107 meq/l, and the urine was still quite positive for acetone. Treatment now consisted of intravenously administered solutions of bicarbonate and lactate Ringer's in glucose with added potassium. By the afternoon of December 16, 1953 the patient appeared much improved and respirations, no longer labored, were 30/min.

In view of the clinical history and symptoms suggestive of cystinosis a tibial puncture was performed and cystine crystals were detected on smears of the bone marrow.

At the time the patient appeared much improved the blood chemistry studies were as follows: carbon dioxide combining power, 15.6 meq/l; sodium, 130 meq/l; chloride, 109 meq/l; and potassium, 2.67 meq/l. Additional potassium was added to the hydrating solutions and the patient appeared to be making a satisfactory recovery from the attack of dehydration and acidosis. Two minutes after the last
clinical appraisal, at which time the child's condition was thought to be good, the patient developed a state of profound collapse and died suddenly, less than 36 hours after admission.

**Necropsy Findings:** At necropsy cystine crystals were found in the spleen, liver, kidneys, lymph nodes, pancreas, thymus, and adrenal glands, all of which had previously been preserved in absolute alcohol.

**Case 2**

**Past History:** F.T., the brother of patient D.M.T. (Case 1), was born on September 21, 1952, by a normal delivery following a normal pregnancy. His birth weight was 3.3 kg and body length 51 cm. The neonatal course and subsequent developmental attainments were thought to be normal. Like his sister he apparently gained in weight until approximately 9 months of age. From 9 months of age until the time of admission the infant had difficulty gaining weight and his estimated weight at the age of 14 months was thought to be 7.0 kg. On direct questioning it became quite apparent that this child, like his sister, manifested a capricious appetite and exhibited an extreme thirst. He did not relish solid foods but drank as much as 2 to 3 quarts of evaporated milk formula per day. This child also had numerous episodes of non-projectile vomiting which the parents attributed to upper respiratory illnesses or to the eruption of teeth. Constipation was not a feature with this child as it was with patient D.M.T. (Case 1).

Although a previous history had indicated that this patient was thought to be in good health, the current story casts some doubt upon the accuracy and validity of that observation. For the past 5 months this patient had many bouts of unexplained fever, frequent colds and sore throats. Approximately 10 days before admission to the hospital the patient had an episode of mild diarrhea which persisted for 3 days. During this period he was quite anorectic and drank only 1 quart of milk per day instead of his usual 2 quarts, despite increasing thirst. The parents thought he had lost some weight during this period and he appeared somewhat dehydrated. The diarrhea gradually ceased and dehydration improved somewhat. He was restless and irritable, however, and developed an intermittent fever which was still present the day of admission to the hospital.

**Physical Findings:** Upon admission to the pediatric service on December 16, 1953, the temperature was 37.8°C, pulse 130/min and respirations 30/min. The initial observations revealed an irritable and somewhat asthenic 14-month-old male who was in no acute distress. The head measured 44 cm and there was a suggestion of bossing. The anterior fontanel was still open. The body length was 71.2 cm and weight 7.3 kg. The skin and mucous membranes were somewhat dry and there was a minimal loss of skin turgor and elasticity. A rachitic rosary was obvious on inspection and palpation. There was no obvious hepatic or splenic enlargement and lymphadenopathy was not detected. The remainder of the physical examination was not remarkable.

**Laboratory Findings:** The laboratory studies were as follows: The hematocrit was 30%, erythrocytes numbered 4,690,000/mm³, hemoglobin 13 gm/100 ml, and total leukocytes 19,400/mm³, with the differential of 12% segmented polymorphonuclears, 84% lymphocytes, and 4% monocytes. The urine was grossly cloudy, and the urinalysis revealed a trace of sugar, albumin, and acetone. Specific gravity of the urine was 1.008, with a pH of 5.0. The blood urea nitrogen was 14 mg/100 ml and blood sugar 88 mg/100 ml. The initial carbon dioxide combining power was 13.0 meq/l, chloride 105 meq/l, and potassium 3.5 meq/l. Cystine crystals were not detected in the urine. A roentgenographic study of the chest and long bones revealed some flaring at the ends of the ribs, with definite cupping of the epiphyseal ends of the distal radius, ulna, tibia, and fibulas.

Because the diagnosis of cystinosis was established in the sibling, and because the patient's symptoms, physical findings, and laboratory studies were suggestive of the disorder, a tibial bone marrow puncture was performed. Examination of the smears of aspirated bone marrow disclosed definite clusters of crystals, which were doubly refractile and compatible with cystine crystals.

**Therapy and Course:** Treatment initially consisted of parenteral fluids containing lactate, glucose and water, and added potassium. Within 24 hours he appeared to be much improved, less irritable, and anxious and willing to resume oral feedings. During the next few days he consumed enormous quantities of skimmed milk formula, orange juice and variable amounts of Shohl's citric acid-sodium ci-
trate mixture. There was some improvement in acid-base balance with an increase in carbon dioxide combining power to 16 meq/l and a decrease of the chloride in serum to 91.3 meq/l; sodium was 129 meq/l; the potassium, however, was 2.5 meq/l. The feeding regimen was discontinued when the patient refused to take fluids, vomited on occasion, and developed a fever of 39.4°C. He became somewhat dehydrated and irritable and it was again necessary to utilize parenteral fluids. With this regimen there was some obvious clinical improvement for the next few days, but on December 24, he reverted to the clinical state as described on admission to the hospital.

Despite parenteral fluid therapy, the carbon dioxide combining power at this time was 12.7; chloride, 146; sodium, 161; and potassium 2 meq/l. The temperature rose to 40°C and the clinical condition was somewhat desperate. Subsequently the infant vomited on several occasions and in one instance the vomitus was described as "coffee ground" in color. Five hours after the last episode of vomiting the patient was more alert and his clinical condition much improved over the previous 24-hour period. The temperature was 37.8°C and once again he was anxious and able to tolerate fluids by mouth. On December 25, 1953, 9 days after admission to the hospital and at a time when he appeared to be improving clinically, he had an episode of gasping respirations and died quite suddenly.

Permission for necropsy was not granted.

Case 3

Past History: E.T., a sister of the two deceased patients, was born on June 21, 1957, by a normal delivery following an uncomplicated pregnancy. The birth weight was 3.3 kg and the neonatal course and development were considered normal.

When knowledge of this pregnancy was apparent it was hoped that this infant could be examined shortly after birth for amino-aciduria and for the presence or absence of cystine crystals in the bone marrow. Unfortunately, as a result of the experience with the two other siblings and a so-called "psychologic block" on the part of the parents, this arrangement never materialized.

At the age of 5 months this infant developed symptoms of polyuria and excessive thirst. From this age until 16 months it was apparent that the child was not gaining weight well and appeared small, pale and thin.

Laboratory studies done elsewhere revealed a moderate anemia and a carbon dioxide combining power of 13 meq/l. As a result of these findings the child was referred to Jefferson Medical College for evaluation.

Physical Findings: The patient was seen in the outpatient clinic on July 7, 1958. At this time the weight was 7.4 kg and the body length was 71 cm. She was pale, thin, and could not walk alone. There was obvious bossing of the skull and definite evidence of a rachitic rosary. The wrists were somewhat "knobby." Hepatosplenomegaly and lymphadenopathy were not present. Permission was only granted for roentgenographic studies and bone marrow aspiration: examination of the long bones confirmed the clinical impression of rickets; cystine crystals were found quite readily in a number of preparations of bone marrow.

For the last 10 months this patient has been treated at home with Shohl's citric acid-sodium citrate mixture and high doses of a preparation of vitamin D. She is gaining weight slowly, is active and has walked alone without support since the age of 19 months.

Discussion

Previously published reviews on the general subject of cystinosis by others,11-12 preclude such a discussion in this paper. The reader is urged to read these excellent monographs for a complete and detailed account of this syndrome.

The three children with cystinosis included in this report are of particular interest in that they represent the entire sibship of unfortunate parents. In all three patients the diagnosis of the disorder was made during life by the demonstration of typical cystine crystals in the bone marrow and confirmed by paper chromatography of the urine in the two deceased children.

A search of the literature has failed to disclose the proved occurrence of this syndrome in more than two children in any single family. In fact, 12 living siblings of 8 affected patients have been investigated and among these only one child was found who was a typical example of cystinosis.13 The
same authors also studied the case histories of 7 additional siblings of these affected patients who were dead at the time of their investigation and assumed that 4 of the 7 dead siblings probably died of cystinosis. Although the case histories could be suggestive there was no empirical proof to substantiate this assumption. Similarly, in a report\(^1\) of two brothers with cystinosis, it is mentioned that two sisters of this family who had previously died had histories that would suggest they also had the disease. While this is entirely possible no evidence was presented to confirm this conclusion. Another report\(^6\) of a documented case of cystinosis in an 11-month-old male infant suggests that four dead sisters of this patient probably suffered from the same disease while one sister was alive and well. These diagnoses were retrospective and unconfirmed by chemical or necropsy studies.

The involvement of all siblings of this family is unique in that the disorder is thought to be inherited as a simple mendelian recessive character with a theoretic expected ratio of 1:3. Actually, the frequency of this condition in the general population has been estimated to be 1 in 40,000 with a gene frequency of 1 in 200.\(^1\)\(^2\)

The genetic prognosis is then believed to be 1 in 4 for any subsequent child of parents who already have one child with the disease.

Certainly in most instances it would appear that cystinosis is inherited as a recessive gene but Ullrich\(^13\) has reported the condition to be transmitted as a dominant gene. Indeed, from the pedigree presented here, one is tempted to speculate that the gene carrying the disease in this family is dominant and not recessive, as all three children were affected. On the other hand, the gene could still be recessive and this sibship may represent three consecutive homozygotic recessives in one family.

Cystinosis has never been reported in different generations of the same family. In fact, it has been shown\(^1\)\(^2\) that chromographic studies of 138 urine specimens of families of 8 children affected with this disease failed to disclose amino-aciduria or glycosuria. Repeated urine specimens from the parents of the three children reported here were also investigated for amino-aciduria and glycosuria with negative results.

Similarly, although the incidence of consanguineous marriages would appear to be increased in families affected with cystinosis, this was not true in this family.

**Demonstration of Cystine Storage**

The diagnosis of cystinosis in the three siblings was established in vivo with the demonstration of typical cystine crystals in aspirated samples of bone marrow. Certainly the clinical picture presented by these patients was suggestive of the disease but final proof rested on the demonstration of cystine storage. Several authors\(^5\)\(^6\)\(^1\)\(^2\) have indicated that the in-vivo demonstration of crystals is most readily accomplished by a lymph node biopsy and that examination of the bone marrow for crystals may be disappointing. While it is true that cystine crystals are not evenly distributed in samples of aspirated bone marrow, they do tend to form clumps or aggregates and are not difficult to locate even under low-power magnification. It is believed that the disappointment encountered by others with the use of bone marrow aspirates for cystine crystals may not necessarily be related to the abundance or paucity of crystals but perhaps to technique. Actual clumps and isolated crystals may not be visualized in stained smears of aspirated marrow if the amount of light passing through the microscope is too intense. Figure 1 is a stained specimen of marrow from patient F.T. (Case 2) with the illumination too intense for comfortable observation. By reducing the amount of light with proper use of the condenser and diaphragm, cystine crystals are readily apparent, even under low-power magnification. Figure 1b is the identical sample and microscope field as Figure 1a but with illumination reduced.

It would appear that examination of aspirated specimens of bone marrow for
cystine crystals can be quite satisfactory and has some advantage over lymph node biopsy or slit-lamp microscopy. Children with cystinosis are frequently acidotic and hypokalemic with clinical features that make them poor candidates for anesthesia or operative surgery. Furthermore, if lymph node biopsy is performed, caution must be exercised that the removed tissue be preserved in absolute alcohol in order to preserve the cystine crystals. The crystals are soluble in formalin, hydrochloric acid and ammonia and additional loss of cystine crystals can occur during the staining process with hematoxylin and eosin. Although slit-lamp microscopy is satisfactory for demonstration of cystine crystals, this procedure requires a co-operative patient and an experienced examiner.

It is certainly apparent that the frequency of ante-mortem diagnosis of cystinosis has increased. The true incidence of the disease is yet to be determined, however, and the diagnosis should be suspect in those infants and young children who fail to thrive. Since proof of cystinosis rests on the demonstration of storage of cystine, bone marrow examination properly performed can be quite rewarding and satisfactory.

**SUMMARY**

Three cases of cystine storage disease occurring in one family are presented. In all three patients the diagnosis of cystine storage was established in vivo with the demonstration of cystine crystals in aspirated specimens of bone marrow and confirmed by paper chromatography of the urine in the two deceased siblings. The genetic aspects of the disorder are briefly discussed.

Bone marrow examination, properly performed, is suggested as a satisfactory procedure for the demonstration of cystine storage.
REFERENCES

DER LIQUOR CEREBROSPINALIS IM KINDEL'-
ALTER. Prof. Dr. H. Schönemberg. Stuttgart, Georg Thieme Verlag, 1960, 175 pp., $6.90.

In the first section of this book techniques and hazards of obtaining cerebrospinal fluid as well as the physiology of the production and absorption of cerebrospinal fluid, the significance of the barriers between blood, brain and cerebrospinal fluid are reviewed. Cytology and chemistry of the cerebrospinal fluid are extensively discussed. Non-routine methods like electrophoresis and chromatography of proteins, respectively, and amino acids are given equal consideration. The techniques and methods of the different procedures are described in detail and critically evaluated. A description of the cerebrospinal changes found in different infections and neoplastic diseases of meninges and nervous parenchyma follows. Finally, special characteristics of the cerebrospinal fluid in the neonatal period are mentioned. The book combines adequate and up-to-date information for the practicing physician, as well as for the laboratory worker.

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