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BIZARRE DEFORMITIES IN OFFSPRING OF USER OF LYSERGIC ACID DIETHYLAMIDE*

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Abstract An infant with a rare combination of severe congenital deformities was born to a woman with a history of using lysergic acid diethylamide. Previously described patients bearing a similarity to this infant were of Puerto Rican parents, most of consanguineous marriage, and in none of these cases was use of this drug indicated. The current state of knowledge of the effects of the compound is such that no definite inference can be made about the current case. All reported cases similar to this one appear to have been due to an unusual recessive mode of inheritance or chromosomal aberration.

REPORTED cases of deformed children born of mothers who were users of lysergic acid diethylamide (LSD) are rare. Recently, such an infant was born at Fitzsimons General Hospital. However, the deformities were more severe than those previously reported, being like those seen in a recently described combination of anomalies referred to as spondylothoracic dysplasia. This report is presented not to prove a relation to use of LSD, but to add to the few known cases and perhaps to stimulate reports of others.

Case Report

V.L., a female infant, was the 1st child of unrelated parents, both native-born citizens of the United States. The medical history of the father is unknown. The 19-year-old mother had no past history of serious illness and no prior exposure to ionizing radiation except routine chest roentgenograms. She did smoke cigarettes, the amount unknown, and admitted to the use of LSD on a single occasion at about the time of conception. Early in the 1st trimester, an estrogen preparation was taken to induce menstruation, without success. First-trimester bleeding occurred, which was treated conservatively with medroxyprogesterone acetate. There was no other known or admitted drug usage and no other illness or problem during pregnancy. This was the mother's 1st pregnancy.

After breech delivery, the infant failed to breathe spontaneously, responding immediately to intubation. Examination showed many deformities (Fig. 1). The neck was short, the left hemithorax smaller than the right, and the abdomen protuberant. A thoracolumbar rachischisis was present. There were clubfeet. The fingers appeared longer than normal.

Roentgenograms (Fig. 2) revealed multiple hemivertebras, neural-arch defects and a severe thoracolumbar lordosis that probably caused the apparent protuberant abdomen. The extremities, except for the feet, were normal. Craniolacunia was present (Fig. 3).

At the age of six days the patient had been anuric for 48 hours, with a blood urea nitrogen of 56 mg per 100 ml. A bladder tap yielded normal urine. Continued urinary retention led to a cystogram, which demonstrated a persistent urachus and a rectovesical fistula. The bladder was large and trabeculated (Fig. 2*B*). No outlet obstruction was identified, probably indicating a neurogenic bladder malfunction.

At the age of 40 days labored respirations and cyanosis developed. Death followed a persistent downhill course of 24 hours. Autopsy confirmed the urinary-tract and skeletal abnormalities described above. Other pathological findings were a horseshoe kidney, single midline adrenal gland, Arnold-Chiari malformation, with hydrocephalus, fusion of the frontal lobes of the brain and a bilateral interstitial pneumonia believed to be due to *Pneumocystis carinii*. Chromosome studies gave normal results.

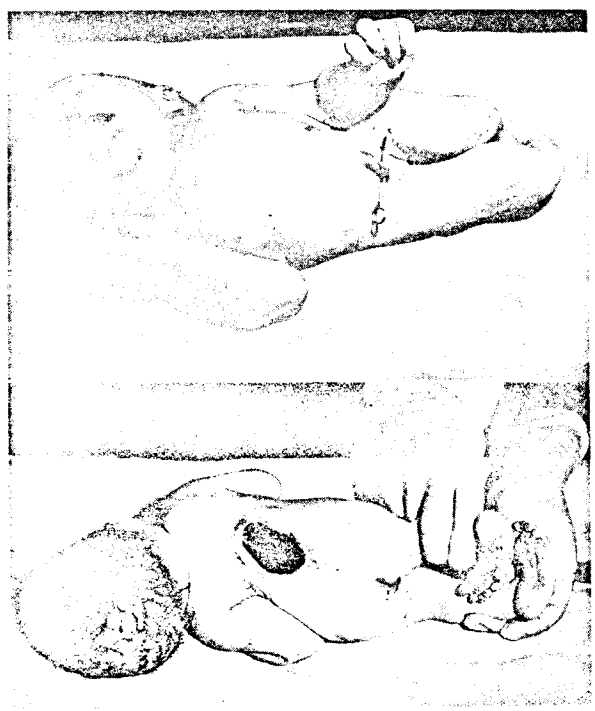

Figure 1. Appearance of the Patient at Birth, Showing the Protuberant Abdomen and Short Neck (Black-and-White Reproduction of a Color Photograph) (A) and the Large Rachischisis and Clubfeet (B).

Discussion

A new syndrome of anomalies of the spine and bony thorax was described by Lavy et al.[1] in 1966. Additional cases were reported in 1969 by Moseley and Bonforte.[2] There were a total of six infants, all of Puerto Rican parents. Four of the infants were of consanguineous marriage. The clinical and roentgenographic features of all patients were rather constant, presenting a bizarre appearance, with short immobile neck, shortened posterior thorax, protuberant abdomen associated with a thoracolumbar lordosis and arachnodacytylous appearance of the digits. Roentgenograms revealed severe segmentation defects of the spine, with close approximation

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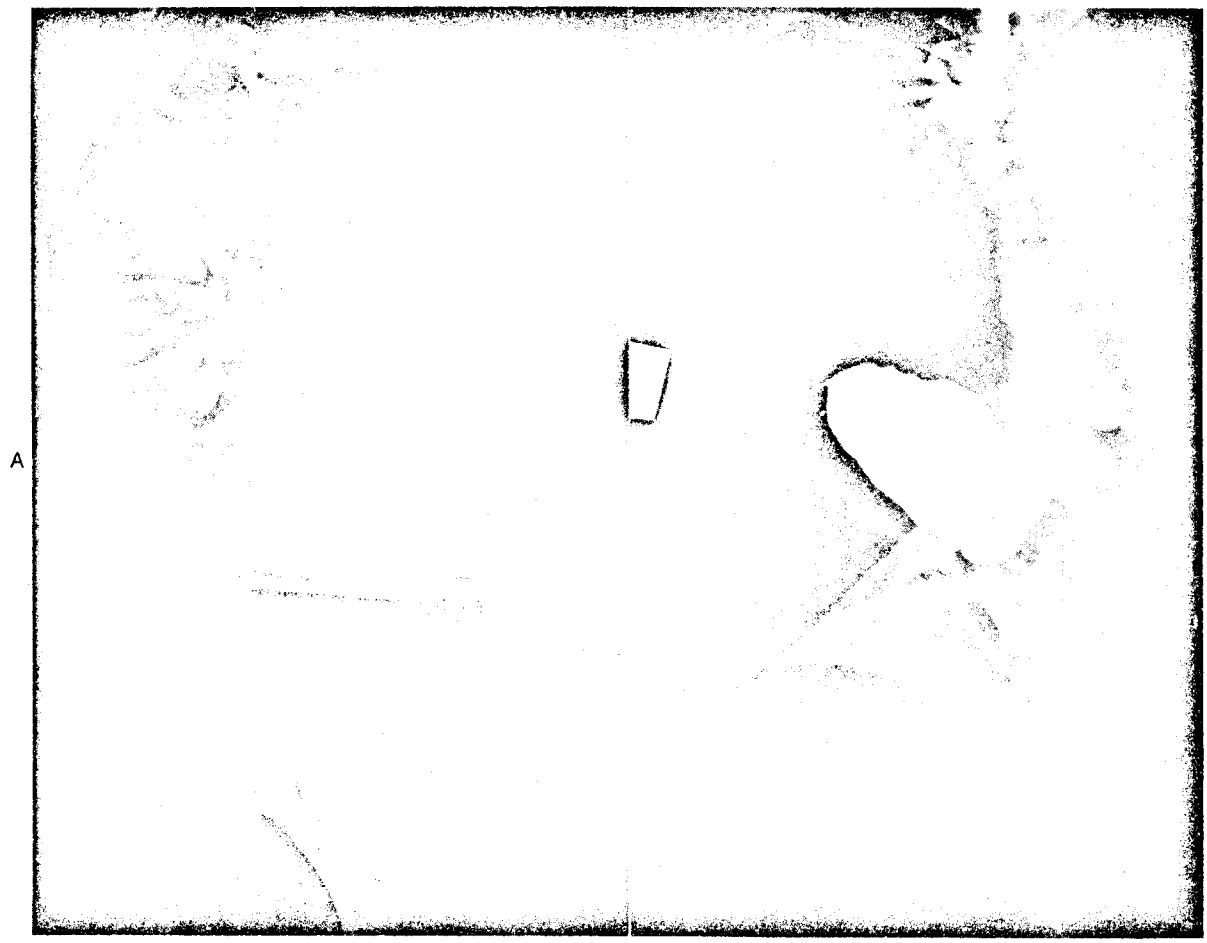

Figure 2. Anteroposterior Roentgenogram (A), Showing Multiple Vertebral Anomalies, with Close Apposition of the Posterior Aspects of the Ribs, and Lateral Roentgenogram (B), Showing Severe Thoracolumbar Lordosis.
The bladder is filled with contrast material, with visualization of urachus. Contrast material in the colon passed from the bladder through a small rectovesical fistula.

Figure 3. Lateral Roentgenogram of the Skull, Showing Craniolacunia.

of the posterior portions of the ribs. The neural arches were widely open throughout the spine. There were numberous hemivertebras and occasional block vertebras. The bones of the extremities appeared normal. None of the infants were noted to have associated skull or urinary-tract anomalies, and no meningoceles were described. All died of respiratory infections within a few months.

The clinical and roentgenographic features of our case are remarkably similar to those previously reported so far as the chest and spine are concerned. The craniolacunia, rachischisis and urinary-tract anomalies have not been described, but information on several of the patients was incomplete and autopsy findings were described in only one.[1] It is logical to assume that rachischisis may occur in the presence of widespread neural-arch defects. Craniolacunia is frequently associated with meningomyeloceles.[3]

The etiology of deformities of this sort remains in doubt, but probably involves an autosomal recessive mode of inheritance in at least some cases.[1] All previous patients were of Puerto Rican parents, where-

as ours is the first known of white parents. The importance of that observation is unknown. The history of ingestion of LSD by the mother is of some interest. There have been two previous reports in which deformed infants, born of mothers who had taken LSD, had relatively mild deformities involving only one extremity.[4,5] There are reports of increased frequency of chromosomal aberrations in users of LSD as well as in their offspring.[6,7] However, the chromosomal and teratogenic effects of LSD are still much in doubt, as indicated in an excellent review of this subject by Smart and Bateman.[8] Additional knowledge is needed before the importance of a history of LSD use can be related to the combination of defects seen in this case, especially with normal results on chromosome studies.

References

1. Lavy NW, Palmer CG, Merritt AD: A syndrome of bizarre vertebral anomalies. J Pediat 69:1121-1125, 1966
2. Moseley JE, Bonforte RJ: Spondylothoracic dysplasia — a syndrome of congenital anomalies. Amer J Roentgen 106:166-169, 1969
3. Shopfner CE, Jabbour JT, Vallion RM: Craniolacunia. Amer J Roentgen 93:343-349, 1965
4. Hecht F, Beals RK, Lees MH, et al: Lysergic-acid-diethylamide and cannabis as possible teratogens in man. Lancet 2:1087, 1968
5. Zellweger H, McDonald JS, Abbo G: Is lysergic-acid diethylamide a teratogen? Lancet 2:1066-1068, 1967
6. Cohen MM, Hirschhorn K, Verbo S, et al: The effect of LSD-25 on the chromosomes of children exposed in utero. Pediat Res 2: 486-492, 1968
7. Hungerford DA, Taylor KM, Shagass C, et al: Cytogenetic effects of LSD 25 therapy in man. JAMA 206:2287-2291, 1968
8. Smart RG, Bateman K: The chromosomal and teratogenic effects of lysergic acid diethylamide: a review of the current literature. Canad Med Ass J 99:805-810, 1968

RENAL TRANSPLANTATION FOR CHILDHOOD CYSTINOSIS*

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Abstract Four cystinotic children with renal failure received a renal allograft from a parent. The follow-up durations for the four patients were eight, 14, 16 and 32 months; final creatinine clearances were 115, 66, 130 and 41 ml per minute per 1.73 m^2 respectively. No decrease in cystine crystals was visible on corneal and bone-marrow examinations. Although the allografts accumulated intracellular cystine, the distribution of cystine was different from that in the natural disease. Cystine crystals were plentiful in interstitial cells of both the patients' original and their transplanted kidneys, but crystals were found in glomerular and tubular epithelial cells only in the original kidneys. Moreover, changes in renal function correlated with complications of transplantation and clinical rejection episodes rather than with the amount of accumulated cystine. So far the Fanconi syndrome does not appear to be developing, and all patients have returned to full activity.

CHILDHOOD cystinosis (cystinosis with the Fanconi syndrome) is a recessively inherited condition characterized clinically by photophobia and progressive renal disease and pathologically by deposition of cystine crystals in many tissues of the body.[1-3] Cystine deposition has been demonstrated in all organs except voluntary, involuntary and cardiac muscles[4]; however, with the exception of the reticuloendothelial system and eye, cystine crystals are more commonly found in macrophages or histiocytes than in parenchymal cells. Amino acid analyses have revealed normal levels of plasma cystine but an 80-fold increase in concentration of cystine in leukocytes.[5,6] Within the cell, the excess cystine appears to be compartmentalized within organelles, which histologically resemble lysosomes.[7] Renal tubular insufficiency frequently begins at six months of age, and the patient usually dies at about 10 years from uremia before severe functional impairment of other organs can be demonstrated. Although many forms of therapy have been tried in childhood cystinosis, none have halted the inexorable progress of the renal disease.[8-10]

The purposes of this study were as follows: to provide life-sustaining function to four children with end-stage renal disease due to cystinosis; to observe the effects of cystinosis on kidneys from heterozygous donors; and to determine the influence of the renal allograft on cystine storage.

Methods and Material

Recipient Patients

The recipient patients were four unrelated children, nine to 10 years of age. Cystinosis was diagnosed in infancy or early childhood, and the patients were managed by sodium and potassium citrate and vitamin D therapy. The diagnosis of cystinosis was based upon the demonstration of generalized proximal tubular dysfunction and cystine-like crystals in the bone marrow and cornea. The diagnosis was further supported by measurement of the concentration of cystine in renal tissue obtained at the time of transplantation. There was no evidence of consanguinity among any of the parents, and the children were mentally normal. Transplantation was

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