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METABOLIC AND CHROMOSOMAL STUDIES IN LEPRECHAUNISM

BY

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Donohue and Uchida (1954) described two sisters with grotesque facial appearance, extreme emaciation, and death occurring under 3 months of age. Based on the assumed resemblance of these children to dwarf cobblers from Irish folklore, the authors called the condition leprechaunism. It is hoped that this term will be changed to a more appropriate name when the underlying lesion is better understood. Until the present time four additional cases of leprechaunism have been described (Evans, 1955; Patterson and Watkins, 1962; Salmon and Webb, 1963). Findings on physical examination suggested to all these investigators an endocrine or metabolic disorder as the possible cause. However, laboratory studies as well as post-mortem examinations in three patients have failed to reveal the basic abnormality. The seventh patient here reported has characteristics typical of leprechaunism. To further the investigation of this condition we have performed most of the metabolic and endocrinological tests currently available, as well as the chromosome studies in the patient and in his parents.

Case Report

E.H. is a 14-month-old boy. The mother was 32 years of age at his birth and she was well except for recurrent episodes of eczematous dermatitis; the father was 35 years of age and healthy. There were no hereditary disorders or the birth of abnormal children in the parents' families. The mother's first pregnancy ended in miscarriage in the third month of gestation; the second, third, and fourth resulted in three normal children, two boys and one girl. The fifth pregnancy, from which the patient was born, was complicated by mild polyhydramnios. The delivery was spontaneous at an estimated 37 weeks of gestation with a birth weight of 3·6 kg. The male infant was noted to be grossly abnormal: his face was grotesque, he had large nares, low-set ears, somewhat sunken and widely-spread eyes, and a short neck. The abdomen was relatively large but the extremities appeared short with ulnar deviation of both hands and equinovarus position of feet. He developed neonatal jaundice but Coombs test was negative and his peripheral blood was essentially normal. Deficient food intake was noted early and he failed to gain weight. At 4 months of age he weighed only 3·5 kg. His nipples appeared enlarged and his body was wasted. Because of difficulty in feeding and generally frail condition he has spent most of his life in hospitals.

Examination at the age of 7 months showed an undersized and emaciated infant of unusual appearance (Fig.). His weight was 4·5 kg., body length 57 cm., and head circumference 43 cm. The skin on the extremities and buttocks was redundant and was thrown into deep folds on his palms. The subcutaneous adipose tissue was almost completely absent. His hair was sparse, the anterior fontanelle was widely open, and the eyes were sunken. The respirations were frequent with intercostal retraction but the chest was clear to auscultation. The heart rate was 116 a minute with a faint systolic murmur which was considered to be functional. The abdomen was protuberant but liver and spleen were not enlarged. He had small umbilical and pronounced bilateral inguinal hernias as well as a diastasis of the rectus muscles. Both testicles were present in the lower part of the inguinal canals and their consistency was normal. He looked at faces and followed objects with his eyes from side to side and funduscopic examination was normal. His best performance consisted of briefly lifting his head up about 3 inches from the mattress while in prone position. Muscle strength was greatly deficient throughout but muscle tone was normal. Tendon reflexes were present and equal, and plantar responses were predominantly flexor. He was weaned from tube feeding, and vigorous but largely unsuccessful attempts were made to increase his weight. There has been some progress, however, in his motor and mental development.

At 14 months of age he was readily turning over and was able to keep his head and chest up while supporting himself on his forearms in prone position. He keenly observed the activity around him showing jealousy if attention was given to the other child in his room and smiled occasionally in response to appropriate stimulation. However, he gave no evidence of understanding spoken words or gestures. In spite of all efforts to increase his food intake and in spite of a well-balanced

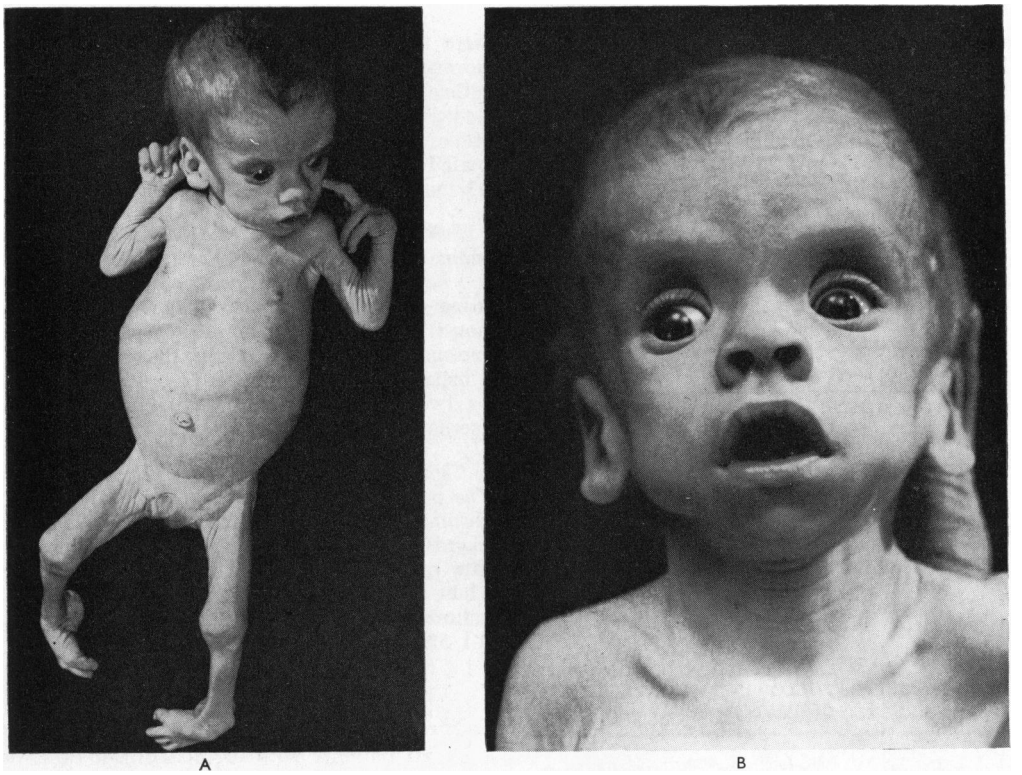

FIG. A and B.—Photograph of the patient at the age of 7 months. Note low-set ears, sunken eyes, deformity of feet, and extreme emaciation.

diet, his weight was only 5 kg. and his height 64 cm. Persisting failure to gain weight was puzzling, especially as there was no evidence that he was losing protein and sugar in urine or fat and protein in the stools. He was subject to frequent staphylococcal infections of the skin and eyelids.

Laboratory Investigations. Routine urinalysis and haemogram were normal on repeated examination. BUN was 17 mg., urinary total α-amino nitrogen was 9 and 7 mg./24 hours on two occasions; quantitative estimation of amino acids in urine (Spinco amino acid analyser) gave normal values. Liver function tests were largely negative. Plasma electrolytes as well as the results of serum protein and γ-globulin electrophoresis were normal. Serology was negative. Electrocardiogram and electroencephalogram were both within normal limits. Radiographs of skull, chest, and skeleton were normal except for a retardation of bone-age and equinovarus deformity of feet. Intravenous pyelogram was normal.

Carbohydrate Metabolism. Blood glucose levels varied from normal to low depending on the duration of fasting. This is well demonstrated in Tables 1 and 2. Similarly, the adrenaline and glucagon tests were normal if he

TABLE 1

ORAL GLUCOSE TOLERANCE TEST (2·2 g./kg. body weight) AT 8 MONTHS OF AGE FOLLOWING A FAST LASTING 10 HOURS

	Blood Sugar Levels
Fasting	33
At 30 min.	92
At 1 hour	120
At 2 hours	141
At 3 hours	46
At 4 hours	42

Blood sugar levels are in mg./100 ml.

TABLE 2

GLUCAGON TEST (1 mg. intramuscularly), AND L-LEUCINE TEST (0·15 mg./kg. body weight orally) AT 8 MONTHS

Glucagon Test (7 hours fast)		L-Leucine Test (10 hours fast)	
Fasting blood sugar	61	Fasting blood sugar	43
15 min.	110	20 min.	38
30 min.	129	40 min.	39
60 min.	129	60 min.	38
		80 min.	42

Blood sugar levels are in mg./100 ml.

fasted for 6 hours and deficient if he fasted for 10 hours (Table 3). Combined insulin-adrenaline test showed excessive and prolonged fall of glucose after insulin and a slow response to adrenaline as compared with values in a normal child (Table 5). The L-leucine tolerance test was not associated with a fall of plasma glucose (Table 2).

TABLE 3

RESULTS OF ADRENALINE TOLERANCE TEST (0·15 mg. subcutaneously) AT 8 MONTHS; FIRST, WHEN THE PATIENT WAS FASTING FOR 10 HOURS, AND TWO DAYS LATER AFTER FASTING FOR 6 HOURS

	Fasting 10 hours	Fasting 6 hours
Fasting blood sugar	32·5	41·3
15 min.	—	56·1
30 min.	35·2	54·4
45 min.	—	53·0
60 min.	35·3	55·2
90 min.	36·0	51·0
120 min.	35·2	—

Blood sugar levels are in mg./100 ml.

TABLE 4

VALUES OF PLASMA LIPIDS ESTIMATED ON THREE DIFFERENT OCCASIONS FOLLOWING VARIABLE LENGTH OF FAST

	Age 8 months: 11 hours' fast	Age 9 months: 8 hours' fast	Age 14 months: 7 hours' fast
Total lipids (mg./100 ml.)	338	396	573
Cholesterol (mg./100 ml.)	105	146	192
Phospholipids (mg./100 ml.)	139	166	196
Triglycerides (mg./100 ml.)	113	107	212
TFA (μg./100 ml.,) ..	702	745	1,020
FFA (μg./100 ml.) ..	199	88	86

TABLE 5

INSULIN (0·25 u./kg. body weight subcutaneously) AND ADRENALINE (0·15 mg. subcutaneously) TOLERANCE TESTS AFTER 5 HOURS OF FASTING IN THE PATIENT, AND AFTER 10 HOURS OF FASTING IN A NORMAL CONTROL INFANT (Plasma glucose is in mg./100 ml.)

	Patient	Normal Control Infant
Fasting blood sugar	70	85
Insulin		
30 min. later	49	58
60 min. later	42	59
90 min. later	47	62
2 hours later	37	69
Adrenaline		
30 min. later	41	76
60 min. later	56	88

Lipid Studies. Serum lipids after 11 hours of fasting were low, especially cholesterol, but the values were normal after 7 hours of fasting (Table 4). Quantitative estimations of fat in stools collected on 9 consecutive days and divided into 3-day samples gave consistently normal values of 2·1 to 2·5 g./day. The fat intake during this period varied from 20-30 g. daily. Blood vitamin A was 33 units and carotene was 35 units/100 ml.

Endocrinological and Other Studies. Protein-bound iodine (PBI) was 8·5 μg./100 ml.; urinary 17-ketosteroids 0·5 mg./24 hours; urinary oestrogen 8 μg./24 hours, and urinary gonadotrophins less than 3 mouse units per 24 hours. Human growth hormone in plasma was 7 mμ/ml. (normal or slightly raised). Sex chromatin was typical of a male. Alkaline phosphatase was 12 and 14 K-A units on two occasions. Urine was negative for mucopolysaccharides.

Chromosome Studies in Short-term Blood Cultures. The patient and his father had a modal number of 46 chromosomes and normal karyotypes. The mother had likewise 46 chromosomes; however, they exhibited a high rate of chromatid- and chromosome-type of breaks. Thus, among 80 mitoses scored in three separate blood cultures there were 19 (24%) breaks encountered (normal 0-1·5%).

Discussion

There was relatively little laboratory work done on the two patients with leprechaunism described by Donohue and Uchida (1954), but the authors provided detailed records of necropsy examination. Two patients of Evans (1955) were alive at the time of his report. However, his second patient (Case 2) did not have features common to other patients with leprechaunism and probably should not be included in this group. The patient of Patterson and Watkins (1962) is still alive and the authors performed a considerable number of laboratory studies. The patient of Salmon and Webb (1963) died at age of 7 months and a detailed necropsy report is available.

The main unifying features of these patients including the present child consist of a grotesque and old facial appearance, dwarfism, extreme emaciation, almost complete failure to gain weight, and mental and motor retardation. The facial characteristics include low-set and generally large ears, beaked nose with flaring nostrils, widely-spaced eyes, thick lips, mostly open mouth, and short neck. Among less consistent physical findings are enlargement of breasts and external genitalia and a variable degree of hirsutism.

The following is the synopsis of the laboratory findings pertinent to studies of endocrine and metabolic disorders in these patients. Low and prolonged response to insulin was noted in all 3

children in whom this test was performed; low fasting blood sugar levels were recorded in most but not all patients. Alkaline phosphatase was low in patients of Patterson and Watkins (1962), Salmon and Webb (1963), and ours, but the values were not known in other cases. Retarded bone-age was noted in all, but this may be a secondary finding which depends on grossly deficient nutritional state and poor motor activity. Urinary amino acids were estimated in 4 patients; in 2 of these they were normal and in 2 raised. 17-ketosteroids were determined in 5 patients and they were normal in all. Urinary oestrogens in Case 1 of Evans (1955) and in the present patient were normal. Urinary gonadotrophins and plasma growth hormone in our patient were within normal limits.

Results of post-mortem examination in 3 patients and organ biopsies in another 3 can be stated as follows. The brains in the 2 children of Donohue and Uchida (1954) were normal, whereas the patient of Salmon and Webb (1963) had severe malformation of the brain in a form of agyria of cerebral hemispheres and rudimentary cerebellum; no histological details are given. Examinations of the pancreas in 4 cases (one of which was biopsy) showed hypertrophy of islets of Langerhans in 3 and normal histological structure in one (Evans, Case 1). The liver was examined histologically in 5 patients: no abnormality was found in 2 biopsy specimens, and in 3 patients who died the lesions were largely unspecific and consisted of focal degeneration or necrosis. In Donohue and Uchida's (1954) patients there was in addition focal increase of glycogen and iron deposits. Ovaries were examined in 3 patients and in all cyst formation was present; in 2 male patients histological studies of the testicles were considered to be normal. Kidneys showed dilatation of tubules in 3 patients who came to necropsy. The pituitary gland was reported as normal in 2 patients and as showing absence of D basophil cells in the patient described by Salmon and Webb (1963). Thyroid, thymus, and other tissues did not disclose any specific abnormality of note. Thus, even with the aid of the necropsy and biopsy examination no uniform abnormality could be demonstrated. Moreover, it appears that we might be dealing rather with a syndrome than with a disease entity. For instance, the patient of Salmon and Webb (1963) had severe cerebral malformation which could account for retardation of development and deficient growth, whereas the brains in the patients of Donohue and Uchida (1954) were normal.

Having repeated carbohydrate and lipid studies in our patient at various occasions, we came to the conclusion that the values were within normal limits or close to normal limits when the fasting period was in the range of 6-7 hours; when the fasting was extended to 11 hours most of the glucose and lipid reserves appeared depleted, as indicated by their low blood levels (Tables 1 and 4). It is evident that the biochemical and endocrinological studies performed in this patient, as well as the results of tests reported by other investigators, did not disclose any consistent metabolic abnormality. However, a possibility of a generalized 'dyscrasia' of a kind seen in mongolism cannot be denied. At the present time we can distinguish only the very gross chromosomal abnormality. Most inversions and small deficiencies of chromosomes in man generally escape detection.

The abnormalities found in the chromosomes of the mother were of two types: the first consisted of random chromosome breaks in about 6% of the mitoses; the second consisted of a 'weak' region involving long arms of the same chromosome, which led to high frequency breaks (about 18%) in this segment. The first type of abnormality is commonly seen in the peripheral blood of individuals exposed to radiation (Tough, Buckton, Baikie, and Court-Brown, 1960; Bender and Gooch, 1962; Buckton, Jacobs, Court Brown, and Doll, 1962); the second type of chromosome abnormality is complex and it will be the subject of a separate communication. On questioning the mother, it was disclosed that she had received x-radiation treatments for eczematous dermatitis. Thus, in 1947 at the age of 16 years she was given 5 irradiations to both ankles, in 1951 3 irradiations to the neck and back of her head, between 1956 and 1957 15 irradiations to various parts of her body, and in 1964 4 irradiations to both hands and wrists. Using *Depth Dose Tables for Use in Radiotherapy* (Scientific Sub-Committee of the Hospital Physicists' Association, 1961), the radiation factors supplied by the respective physicians were individually converted into skin dose and then summed up to arrive at a total skin dose of 1,550r. All radiations were estimated as being for soft tissue and therefore the dose to the bone-marrow and the lymphoid tissue must be reduced by a factor of about 0·6. Although the history of radiation may tempt speculations, the evidence of the present data does not permit us to ascribe the clinical syndrome of the offspring to the chromosomal aberration encountered in the maternal blood.

Summary

An infant with persisting failure to gain weight is described under the title of leprechaunism. Scanty literature pertaining to this condition is reviewed. Exhaustive biochemical and endocrinological studies conducted in this patient added new data but failed to reveal the cause of the underlying abnormality.

The blood levels of certain constituents were subnormal when fasting extended over 10-11 hours, but these values were within normal limits when the blood was drawn after 6 to 8 hours of fasting. The child has 46 chromosomes of normal appearance, but his mother has a high incidence (24%) of chromosome- and chromatid-type breaks. She has received repeated x-ray treatments to various parts of her body for eczematous dermatitis during the past 14 years.

Addendum

When this article was ready for publication, two sisters with leprechaunism were reported from Hungary (Kálló, Lakatos, and Szijártó, 1965); they both died under 6 weeks of age. As in other females with leprechaunism, their ovaries showed follicular maturation with cystic formation. In general, the clinical and pathological findings corresponded closely to those described previously.

Sincere thanks are due to my associates and colleagues at the National Institutes of Health for stimulating discussions during the study of this patient. I am especially grateful to Dr. L. Laster for quantitative estimation of fat in stools and to Dr. J. Roth for the analysis of plasma growth hormone. Dr. S. Suddarth referred this child to us and supplied valuable clinical and laboratory data on the initial six months of life.

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