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LEPRECHAUNISM IN TWO TURKISH PATIENTS*

*Aytemiz Gürgey MD***, Safiye Göğüş MD***, Ümit Saatçi MD***
*Nihat Bilginturan MD***, Nurşen Yordam MD***, Turgay Coşkun MD***
*Süheyla Özkutlu MD***, Nilüfer Şahin MD****

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We report two cases of Leprechaunism with the classical features. The first case had hyperglycemia and severe hyperinsulinemia. The postmortem examination of the second child revealed enlargement of both ovaries, islet cell hyperplasia in the pancreas, and cholestasis and paucity of bile ducts in the liver. Cystic changes were noted in the ovaries, and the kidneys contained a few small cortical cysts. Both patients died at early ages.
Key words: leprechaunism, insulin resistance, Donohue syndrome, islet cell hyperplasia.

Leprechaunism is a rare autosomal-recessive syndrome characterized by a gnome-like appearance, decreased subcutaneous adipose tissue, hirsutism, enlarged genitalia, and intrauterine and neonatal growth retardation[1-10]. Associated metabolic abnormalities include insulin resistance with hyperinsulinemia and postprandial glucose intolerance[11-18]. Mutations in the insulin receptor gene have been described in patients with leprechaunism, and most have homozygote missense or compound heterozygote mutations[15-17]. However, homozygous nonsense mutation in the insulin receptor gene has also been described in an infant with leprechaunism[15]. These patients are also subject to episodes of paradoxical fasting hypoglycemia, which may be due to poor availability of gluconeogenic substrates[1]. As far as we know, this phenomenon is rare in Turkey[18].

Here, we report two unrelated Turkish patients with this syndrome, one of whom was diagnosed with leprechaunism on postmortem examination.

Case Reports

Case 1

A three-month-old male was referred to Hacettepe Children's Hospital for evaluation of hyperglycemia. His history revealed that he was the third product of a marriage between first cousins, and his sister had died of an ovarian cyst following surgery at the age of eight months. His birth weight was 1800 g. Physical examination revealed findings of leprechaunism including growth retardation, widely spaced eyes, depressed nasal bridge, large ears, gum hypertrophy,

* From the Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.
** Professor of Pediatrics, Hacettepe University Faculty of Medicine.
*** Research Assistant in Pediatrics, Hacettepe University Faculty of Medicine.

prominent nipples, hypertrichosis, lack of subcutaneous fat, decreased muscle mass, distended abdomen and large genitalia (Fig. 1). His weight was 2700 g, length 51 cm and head circumference 34.5 cm, all being below the 5th percentile. The liver was palpated four centimeters below the costal margin. The left ventricular posterior wall thickness was found to be nine mm (normal 2.3-3.7 mm), the interventricular septal thickness 11 mm (normal 2.4-3.6 mm), and the left ventricular systolic functions were normal on two-dimensional echocardiography. Doppler echocardiography revealed mitral regurgitation (3.28 m/sn). Renal ultrasound revealed bilaterally enlarged kidneys and the presence of medullary nephrocalcinosis. He also had mild hypertension. His bone age corresponded to his chronological age. Investigations including complete blood count, total bilirubin, cholesterol, alkaline phosphatase, total protein, albumin, erythrocyte sedimentation rate, vanyl mandelic acid (VMA), creatine clearance, lymphocyte subpopulation, complement components and serum immunoglobulins were normal. The skeletal survey revealed no bony abnormality.

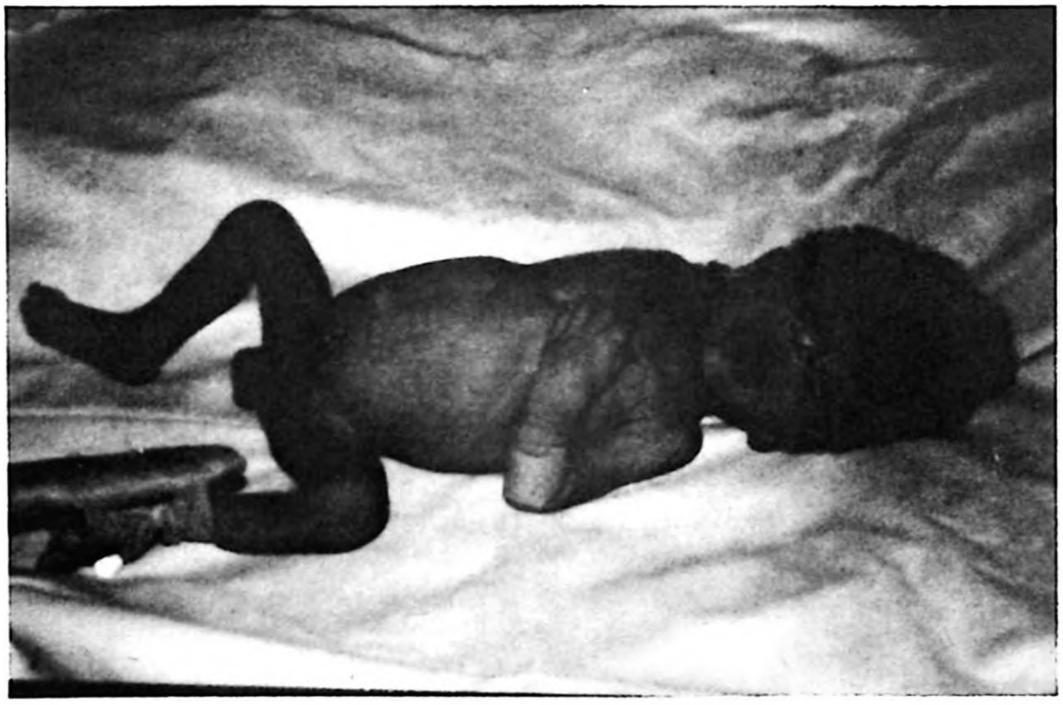

Fig. 1: Appearance of Case 1.

His fasting blood glucose was 348 mg/dl with a simultaneous insulin level of 125 μu/ml (normal 25 < μu/ml). C-peptide was 1.70 pmol/ml (normal < 1.30 pmol). The triglyceride level was 464 mg/dl. He was treated with regular insulin subcutaneously (1 u/kg/day) with no response. Insulin was then administered by continuous infusion intravenously for two days. His insulin requirement decreased gradually and later was given by subcutaneous injection (Fig. 2). The patient unfortunately developed septicemia and died at the age of four months.

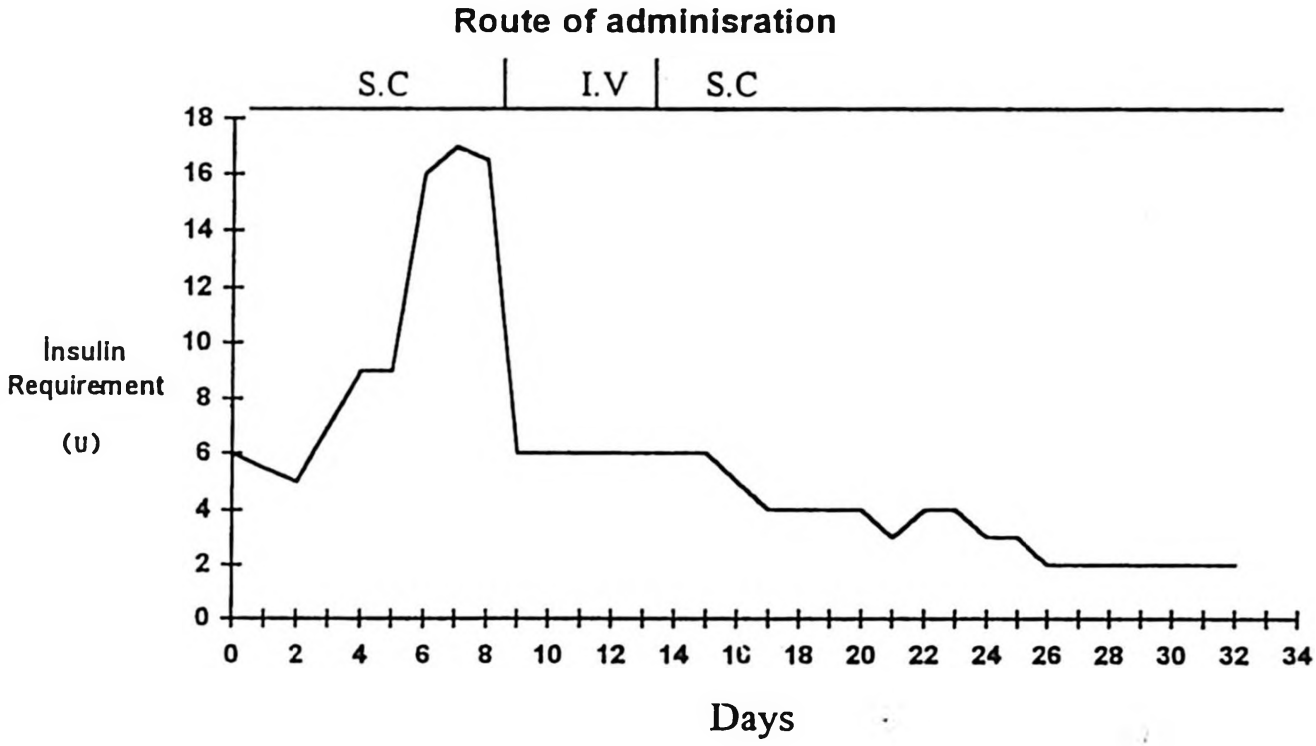

Fig. 2: Insulin requirement of Case 1.

Case 2

A 21-day-old girl was admitted to Hacettepe Children's Hospital for evaluation of a two-week history of abdominal distention and acholic feces. She had been born as the second child to healthy unrelated parents after an uncomplicated term pregnancy and normal delivery. Her birth weight was 1800 g. The first child of the family was healthy and length years old. On physical examination, her weight was 2300 g (< 5^{th} percentile), Length was 43 cm (< 5^{th} percentile) and head circumference was 35 cm (< 10^{th} percentile). She had a peculiar appearance with widely spaced eyes, depressed nasal bridge, facial hypertrichosis especially of the forehead, and decreased subcutaneous tissue. Her eyelids were edematous, and pretibial edema was noted. She also had a distended abdomen and an umbilical hernia.

Results of Laboratory Investigations were as Follows:

Serum total protein 4 g/dl (albumin 2 g/dl), blood glucose 70 mg/dl, alkaline phosphatase 18.9 IU/L (normal 1.5-4.5 IU/L), SGOT 110 IU/L, SGPT 55 IU/L, total serum bilirubin 2.5 mg/dl and direct reacting bilirubin 1.7 mg/dl. The remainder of laboratory investigations including complete blood count, urinalysis, total lipids, cholesterol, blood urea, amino acids and serum α_1 antitrypsin levels were within normal limits. There was a generalized nonspecific aminoaciduria. Prothrombin and partial thromboplastin times were prolonged. Paracentesis

revealed clear ascitic fluid with a protein leves of 1.8 g/dl. Direct Coombs was negative. A search for intrauterine infections was found to be negative. The patient developed a local skin infection and died 10 days after admission. A complete autopsy was performed.

Autopsy findings: Macroscopically there were double renal arteries in the right kidney. The weight of the kidneys was 34 g (normal 18.3 g), while the weight of the pancreas was 5 g (normal 2.1 g). Both ovaries were large for age (Fig. 3). Microscopically emphysema and bronchopneumonia were detected in the lungs. Moreover, hepatocellular and canallicular cholestasis, pseudoglandular transformation of the hepatocyte, extramedullary hematopoiesis, and a mild to moderate increase of fibrous tissue in the portal areas were noted. Paucity of the bile duct was also detected in the portal areas. Iron pigments were present in both hepatocytes and Kupffer cells. Prominent islet cell hyperplasia and hypertrophy of the pancreas were prominent (Fig. 4). There were various degrees of maturation in the ovarian follicles with some cystic changes. Edema was found in the brain tissue. The spleen was congested, extramedullary hematopoiesis and iron pigment were detected and lymphoid follicles were present. There was lymphocyte depletion as well as many cystic and clacified Hassall's corpuscles in the thymus. Lymphoid tissue depletion was not present in the other tissues. Hypertrophy was not found in the myocardial fibris. The kidneys had a few small cortical cysts and congestion; otherwise the histologic appearance was normal. Subcutaneous fat tissue was decreased. No microscopic pathology was detected in the other internal organs. The patient fulfilled the clinical and pathological findings for the diagnosis of leprechaunism.

Fig. 3: Gross appearance of the ovary in Case 2 as compared to age-matched control.

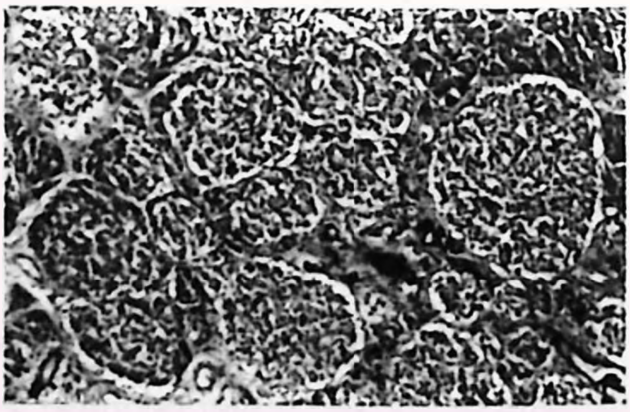

Fig. 4: Hyperplastic islets of Langherhans in the panceras (Case 2). HE x 33.

Discussion

Leprechaunism (Donohue Syndrome) was initially described as dysendocrinism by Donohue in 1948[1]. In 1954, a similar child was born to the same family, and

Donohue et al.[2] proposed the term "leprechaunism" for this disorder. Since then only a few patients with the syndrome have been studied extensively. Our patients had clinical, biochemical and pathological findings for the diagnosis of leprechaunism. Another genetic syndrome with insulin resistance is congenital generalized lipoatrophy[20]. Although these two syndromes share some features such as hypertrichosis, cardiomyopathy, hypertriglyceridemia, hyperglycemia and growth retardation, a syndrome is defined based on the presence or absence of specific clinical features. For example, in lipoatrophic diabetes, there is atrophy of subcutaneous fat. Fasting hypoglycemia, hyperglycemia/hyperinsulinemia after meals, and multiple abnormal features are specific to leprechaunism[21].

At least 52 patients with this syndrome had been reported as of 1993[11]. There are fever than 30 autopsy reports in the literature[1-10, 13, 21-22]. A common pathologic finding is the presence of large, cystic ovaries in females[1-10]. Enlargement of the testis and penis in some male patients and hyperplasia of pancreatic islet cells have been described[1-10]. In a review of 19 autopsy cases of leprechaunism, 12 cases (63%) had pancreatic islet cell hyperplasia[20]. The ovaries and pancreas of Case 2 had these histopathologic features while the sister of Case 1 had died following surgery for ovarian cysts. Hepatic pathology in leprechaunism is not uniform. The histologic appearance of the liver may be normal[3, 5], although, cholestasis bile duct proliferation and hemosiderosis have been detected in the liver of some cases[1, 2, 4, 6-8]. In this disorder, multiple small nodules composed of large, pale foamy hepatocytes with large quantities of glycogen and little fat and iron have been also described in the liver[2, 6]. David and Goodman[22] reported four infants who had hepatic pathology characterized by marked hemosiderosis, cholestasis with severe diminution of the number of portal intrahepatic bile ducts and formation of bile lakes and pseudoglandular structures in the hepatic lobules. The liver of Case 2 also showed cholestasis, hemosiderosis, increased fibrous tissue and paucity of bile ducts in the portal areas. Recently a case of leprechaunism with a congenital bilateral tumors of the ovaries and cytomegalovirus hepatitis was reported[23].

Kidney enlargement as well as histologically tubular dilatation, calcification with intratubular granules or both, have also been described in leprechaunism[2-4, 6, 10]. Medullary nephrocalcinosis and kidney enlargement were present in Case 1. Recently a 13-year-old girl with leprechaunism who developed hypertension and albuminuria was described, and renal and glomerular enlargement as well as morphometric glomerular changes similar to those seen in patients with diabetic nephropathy were observed[24]. Although the weight of the kidneys in our Case 2 was increased, the histologic appearance was normal apart from congestion and the peresence of a few small cortical cysts. Myocardial hypertrophy has also been described in some cases[10, 12], and was present in Case 1 but not

Case 2. Lymphoid tissue depletion in the lymphoid organs and cystic Hassall's corpuscles have been described in some patients[3-5, 7, 8]. The thymus of Case 2 showed lymphocyte depletion and cystic changes of Hassall's corpuscles.

At the molecular level, leprechaunism is associated with defects in insulin binding, insulin receptor autophosphorylation, and kinase activity[14].

However, recently various point mutations in the insulin receptor gene have been detected, and some patients also have functional abnormalities of receptors for insulin-like growth factor 1(IGF)[14, 15]. It has been suggested that different defects of the insulin receptor and receptor-signaling mechanism may be responsible for this phenotypic heterogeneity of leprechaunism[16]. The selective action of insulin on some tissues may be releated to the density or affinity of the IGF-1 receptor. The ovary, heart, muscle vascular endothelium and kidney have IGF-1 receptors[16, 17]. This could explain the ovarian enlargement, myocardial hypertrophy, kidney enlargement and severe intrauterine growth retardation which are reported in some patients with leprechaunism.

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