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A CASE OF LEPRECHAUNISM WITH CHROMOSOME ABNORMALITY (46, XX, der(21), t(3; 21)(q26 or 27; q22)pat)

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Summary A 20-day-old girl who was diagnosed as leprechaunism had a 46,XX, 21q+ complement. Both of the father and the paternal grand father were carriers of a translocation t(3;21) (q26 or 27;q22). The patient was trisomic for the distal segment of 3q and monosomic for a very small segment of 21q. The karyotype was 46,XX, der(21), rcp(3;21) (q26 or 27;q22). Clinical features of the only reported case of distal 3q trisomy in the literature as well as cytogenetic findings of cases with leprechaunism are briefly reviewed.

INTRODUCTION

In 1954, Donohue and Uchida described two siblings with leprechaunism. The syndrome was characterized by a leprechaun-like face (large low-set ears, hypertelorism, big broad nose, big mouth and hirsutism), large hands and feet, wrinkled skin, stunted growth and mental retardation. Since then, 24 cases of leprechaunism have been reported, including 7 cases in Japan.

CASE REPORT

The patient, a 20-day-old female, was admitted to our hospital. She was the fourth child of a 32-year-old mother and a 35-year-old father. The parents appeared normal and not consanguineous. The first baby was stillborn and the second, a female, died of heart failure on the 15th day after birth. The facial appearance of the second baby is said to have closely resembled to that of the present patient. The 3rd child is a healthy boy and normal in appearance.

The pregnancy was uneventful. The patient was delivered at 40th week of gestation. Her birth weight was 4 kg and crown-heel length was 50 cm. Cyanosis and respiratory distress signs were noted soon after birth.

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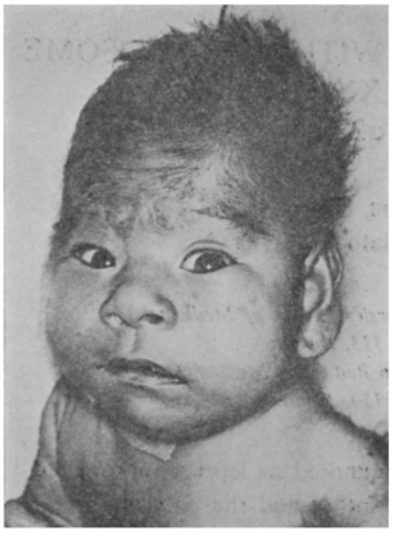

Fig. 1. Patient at 20 days of age, showing typical facial expression of leprechaunism.

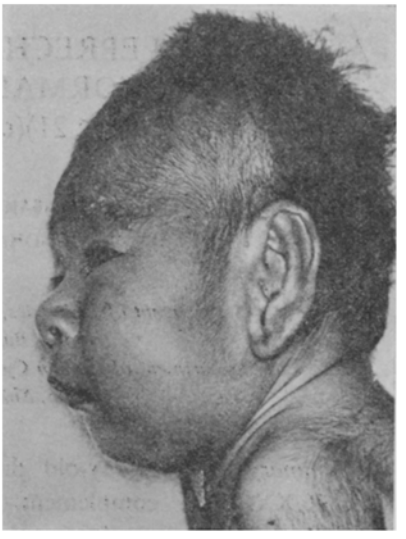

Fig. 2. Side view of the face. Receded chin and big ear are noticed.

On admission, the patient weighed 3.7 kg. The face looked unusual with large eyes, broad nose, large mouth and receded chin. The scalp hair was long and silky and covered the forehead. The neck was very short. Ear lobes were unusually large and preauricular fistulas were present on both sides (Figs. 1 and 2). Cyanosis was noted on the lips and the nail-beds. The subcutaneous fat was meager. The clitoris was enlarged but the nipples were not prominent. The hands and the feet appeared normal. She cried in a large and low-pitched voice. Moderate rough systolic murmurs were audible on the left side of the sternum at the 3rd intercostal space. The abdomen was distended with poor muscular tone. The liver and the spleen were palpable 4.5 cm below the each costal margin.

Laboratory data on admission were all within normal limits except blood gas analysis: pO_2, 44.7 mmHg; pCO_2, 37.1 mmHg; pH, 7.414; HCO_3^-, 23.2 mEq/litre and O_2 saturation, 81.5%.

The respiratory distress and cyanosis did not improve after admission. Chest X-ray showed an enlarged heart shadow and a decreased translucency of the lungs. ECG showed the right ventricular loading. Cardiac catheterisation revealed the presence of atrial septal defect, ventricular septal defect, patent ductus arteriosus and pulmonary hypertension. As the pulmonary flow was gradually increasing, surgical treatments (banding of the pulmonary artery and ligation of the ductus arteriosus) were performed. The postoperative course was extremely good with disappeared cyanosis and improved weight gaining.

At 3 months of age, glycosuria was detected. The oral glucose tolerance test

showed a flat curve of blood glucose, indicating the poor absorption of glucose through the intestine. The intravenous glucose tolerance test was normal, indicating the normal insulin secretion. The insulin tolerance test was also within normal limits. Other hormonal studies showed: T_4, 5.4 μg/dl; ACTH, 190 pg/dl; MSH, 200 pg/dl; urinary 17-ketosteroids, 0.13–1.1 mg/day and urinary 17-hydroxysteroids, 1.0–5.6 mg/day. Plasma lipid levels after fasting of 6 hours were as follows: total lipids, 700 mg/dl; phospholipids, 7.1 mg/dl; neutral fats, 279 mg/dl and free fatty acids, 0.31 mg/dl. Immunoglobulins at 6 months of age were as follows: IgG, 800 mg/dl; IgM, 120 mg/dl and IgA, 130 mg/dl.

At 6 months of age, X-ray films revealed retarded skeletal age with poor ossification of both tibia and carpal bones and hypoplasia of the acetabulum. In neurological examinations, tendon reflexes were slightly accentuated, although abnormal reflexes were not elicited. Muscles were hypotonic and movements of the limbs were fairly stiff. The electroencephalograms were normal and compatible for her age.

In the subsequent course of hospitalization, episodes of high-fever attack lasting for several days were observed about once a month. Her somatic development was almost normal, but her mental one was considerably delayed. During the period several months prior to her death, shw cried loudly when she wanted to get attention or something, stared at anyone talking to her, followed its movements with her eyes and sometimes smiled at it. She could also play with toys, transferring it from one hand to the other, and when a handkerchief was placed over her face, she could take it away immediately. She was able to hold her head steadily but could not sit up alone.

Dermatoglyphic studies revealed 4 ulnar loops and 1 radial loop (4th finger) on the right fingers, and 4 ulnar loops and 1 arch on the left. The *atd* angles of the hands were 47.5° (r) and 45.5° (1). Total ridge count was 67 and simian crease was not seen.

At the age of 9 months, she weighed 8.2 kg and was 70 cm in crown-heel length. There were 4 teeth on the upper jaw and 2 on the lower. The anterior fontanel was measured 2×2 cm, and the posterior was closed. She died of pneumonia. Autopsy was not granted.

CHROMOSOME STUDIES

Chromosome preparations were made from both cultured lymphocytes and skin fibroblasts. In every cell studied, an abnormal Gq+ chromosome was detected. Quinacrine and Giemsa banding revealed that the abnormal chromosome was a number 21 with extra chromosome material attached to the distal end of its long arm (Fig. 3). The chromosome analysis of her parents and their relatives revealed that both her father and paternal grandfather were carriers of a balanced translocation between a No. 3 and a G. By Giemsa banding, the translocation was identified

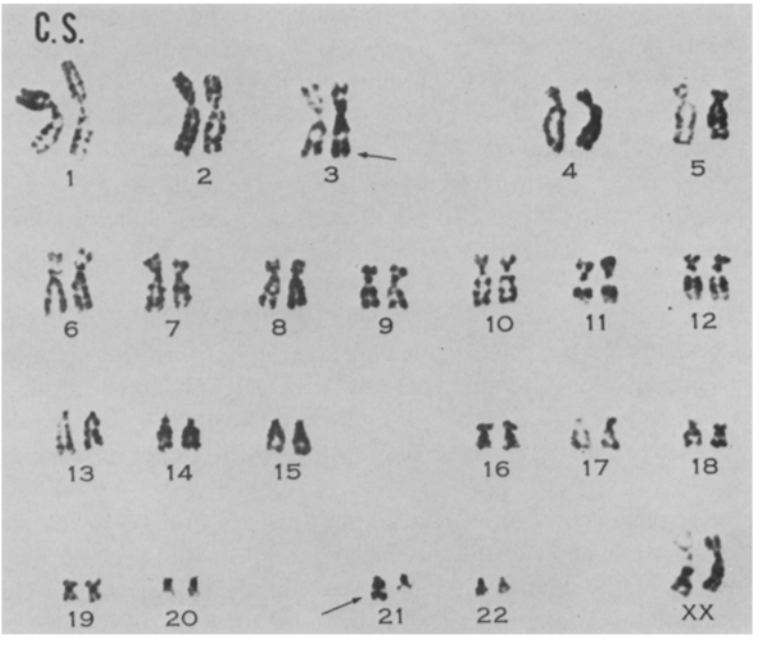

Fig. 3. G-banded karyotype of the patient. Arrows indicate points of exchange.

as rcp(3; 21) (q26 or 27; q22), *i.e.*, the terminal part of the long arm of a No. 3 was translocated on the long arm of a No. 21. Since the patient had two intact No. 3 chromosomes, she was trisomic for the distal segment of the long arm of a chromosome No. 3 and monosomic for the very small segment of the long arm of a chromosome No. 21. The karyotype of the patient was 46,XX, der(21), rcp(3; 21) (q26 or 27; q22) pat according to the Paris Conference (1972). Karyotypes of the mother and siblings were normal. Giemsa banded partial karyotypes of the patient, the father and paternal grandfather are shown in Fig. 4.

DISCUSSION

Twenty-four cases of leprechaunism have been reported including 7 cases in Japan and the present patient. Most of them died in early infancy. Autopsies revealed such prominent features as cystic ovaries, hyperplasia of the Langerhans' islet, hypoplasia of the brain or spinal cord and atrophy of the thymus. Congenital heart disease has been found in two cases (Kuhlkamp and Helwig, 1970; Shimada, 1973). Collapse of aorta (Ferguson-Smith *et al.*, 1968) and persistent left vena cava, absent innominate vein and the presence of both coronary ostia in the posterior sinus of Valsalva (Summitt and Favara, 1969) have also been reported. In our case atrial and ventricular septal defects and patent ductus arteriosus were found by cardiac catheterisation.

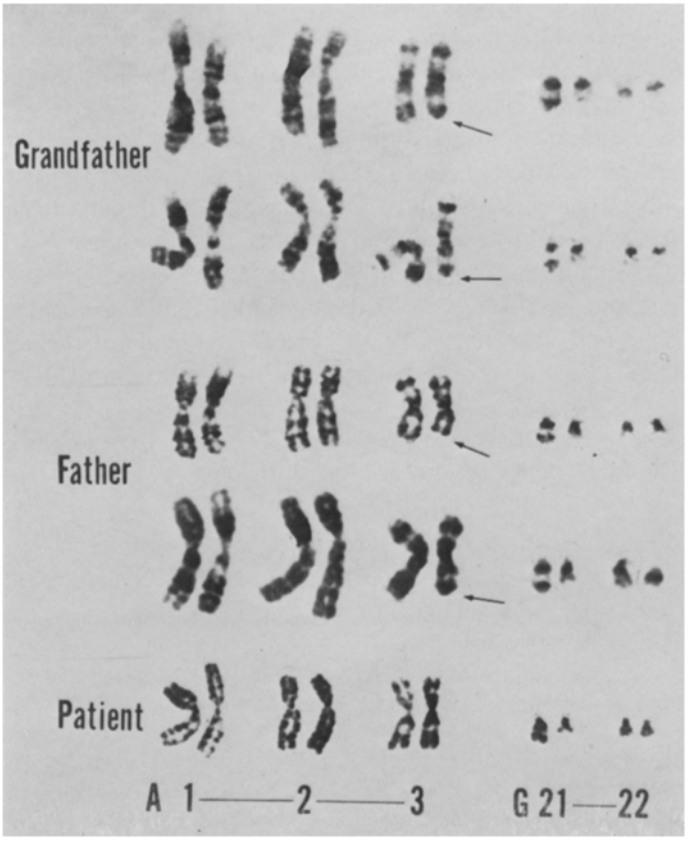

Fig. 4. Partial karyotype of the paternal grandfather, the father and the patient. A and G chromosomes are shown. Arrows indicate der (3) chromosomes.

Although bizarre and multiple deformities in leprechaunism suggest the presence of a chromosomal abnormality, such a finding has been demonstrated only in one case reported by Ferguson-Smith *et al.* (1968). The case was a male infant with a karyotype 46,XY, Cp+. The abnormal metacentric chromosome was observed in both lymphocyte and skin fibroblast cultures.

Leprechaunism has been accepted as a rare Menderian recessive condition. However, he proposed two possible mechanisms in order to explain the presence of the unexpected chromosomal aberration in his patient; 1) the coincidental occurrence of a chromosomal aberration with a homozygous condition, and 2) the expression of the condition in a heterozygote by causing a heterozygous deletion of a normal allele at the leprechaun locus due to the chromosome aberration. He considered the latter possibility which implied that the locus for the leprechaun gene was normally located in the aberrant chromosome and depended on the coincidental

chromosomal deletion of a rare gene in a particular chromosome. He also speculated on the different ways in which the Cp+ aberrant chromosome was transmitted from one of the parents who was a balanced carrier. In his case, however, both parents had normal karyotypes.

In our case, both the father and the paternal grandfather were balanced carriers of a reciprocal translocation rcp(3; 21) (q26 or 27; q22)pat. The patient received the normal No. 3 chromosome and the abnormal No. 21 chromosome from her father, resulting in partial trisomy of the long arm of chromosome No. 3 and partial monosomy of the long arm of chromosome No. 21. We consider that the clinical abnormalities in our case were due to the unbalanced chromosomal translocation, though further studies are necessary to determine whether leprechaunism is an autosomal recessive condition or one of the chromosome abnormalities.

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REFERENCES

Dekaban, A. 1965. Metabolic and chromosomal studies in leprechaunism. *Arch. Dis. Childh.* **40**: 632–636.

Der Kaloustian, V. M., Kronfol, N. M., Takla, R., Habash, A., Khazin, A., and Najjar, S. S. 1971. Leprechaunism, A report of two new cases. *Amer. J. Dis. Child.* **122**: 442–445.

Donohue, W. L. and Uchida, I. 1954. Leprechaunism, A euphuism for a rare familiar disorder. *J. Pediatr.* **45**: 505–519.

Evans, P. R. 1955. Leprechaunism. *Arch. Dis. Childh.* **30**: 479–483.

Ferguson-Smith, M. A., Hamilton, W., Ferguson, I. C., and Ellis, P. M. 1968. An abnormal metacentric chromosome in an infant with leprechaunism. *Ann. Génét.* **11**: 195–200.

Gross-Kieselstein, E., Ben-Galim, E., Amir, N., and Abrahamov, A. 1973. Leprechaunism (Donohue syndrome). *Amer. J. Dis. Child.* **126**: 500–503.

Kálló, A., Lakatos, I., and Szijártó, L. 1965. Leprechaunism (Donohue's syndrome). *J. Pediatr.* **66**: 372–379.

Kuhlkamp, F. und Helwig, H. 1970. Das Krankheitsbild des Kongenitalen Dysendokrinismus oder Leprechaunismus. *Z. Kinderheilk.* **109**: 50–63.

Kuwabara, H. 1973. Leprechaunism (Donohue's syndrome). *J. Pediatr. Practice* **36**: 364–368 (in Japanese).

Morooka, K. 1973. Leprechaunism (Donohue's syndrome). *Brain and Development* **5**: 171–173 (in Japanese).

Patterson, J. H. and Lorraine Watkins, W. 1962. Leprechaunism in a male infant. *J. Pediatr.* **60**: 730–739.

Rogers, D. R. 1966. Leprechaunism (Donohue's syndrome), A possible case, with emphasis on change in the adenohypophysis. *Amer. J. Clin. Path.* **45**: 614–619.

Salmon, M. A. and Webb, J. N. 1963. Dystrophic changes associated with leprechaunism in a male infant. *Arch. Dis. Childh.* **38**: 530–535.

Shimada, N. 1973. Leprechaunism. Rinshoo Shinseijigaku Koza. Kanehara Shuppan, p. 560 (in Japanese).

Summitt, R. L. and Favara, B. E. 1969. Leprechaunism (Donohue's syndrome), a case report.

J. Pediatr. **74**: 601–610.

Tsujino, G. 1968. An autopsy case of leprechaunism. *Acta Pediatrica Japonica* **72**: 1549–1550 (in Japanese).

Uematsu, K., Morimura, Y., Matsumoto, K., Kato, K., Tsujino, G., and Minogawa, J. 1974. Leprechaunism (Donohue's syndrome) Two autopsy cases. *Acta Path. Jap.* **24**: 309–324.