Efficacy of Transplantation of Human Fetal Tissues in Treatment of the Child with Fanconi's Syndrome

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A fundamentally new method of treating children with Fanconi's syndrome using the transplantation of human fetal tissues is outlined below. A positive dynamics is noted in clinical and laboratory manifestations. This is a preliminary report.

Key Words: *transplantation of human fetal tissues; approaches to the treatment of Fanconi's syndrome*

Fanconi's syndrome includes a triad of disorders: hypophosphatemic skeletal abnormalities, generalized renal aminoaciduria, and renal glucosuria [2]. In addition, mental and physical retardation may be noted as well as a lowered resistance to infection, phosphaturia, polyuria, and metabolic acidosis [1].

This disease is known as Fanconi's syndrome or Fanconi-de Toni-Debre syndrome. Fanconi was the first to propose the theory of the "tubular" nature of the disorder and noted the increased urinary excretion of organic acids which could not be identified at that time [3].

The disease is an example of polysymptomatic tubulopathy. Besides the constant characteristic triad, different variants of additional functional dysfunctions may be noted in each case.

There are two forms of the disease. The primary idiopathic form is congenital and has an autosomal recessive inheritance. The secondary syndrome of proximal tubular failure may occur with cystinosis, the hepatorenal form of glycogen disease, Wilson's disease, multiple myeloma, heavy metal poisoning, nephrotic syndrome, etc. [2].

The pathogenesis of symptoms in Fanconi's syndrome is not known. Probably there is an alteration of the enzyme contents of epithelial cells of the renal tubules and altered function of the parathyroid glands. A significant decrease of alkaline phosphatase is found in cells of the proximal renal tubules, making it possible to attribute the decrease of amino acid resorption to impaired phosphorylation.

Treatment should be aimed at the correction of acidosis and the level of potassium in the blood serum and therapy for rickets. A low-salt diet is prescribed. Sodium hydrocarbonate or citrate, combined with potassium citrate in hypokaliemia, is used to eliminate acidosis. High doses of vitamin D support the treatment of rickets. The therapy has to be carried out in repeated courses because discontinuation of the drug often causes relapses of osteoporosis and rickets. As a rule, growth retardation persists. Glucosuria and aminoaciduria are not affected by the therapy [2].

The course and outcome of congenital Fanconi's syndrome is different. Improvement and even recovery occurs in some cases after the age of 8 years. More often this disease is complicated by interstitial nephritis, progressing to the stage of chronic renal failure. The prognosis in the secondary form is largely determined by the course of the main disease.

Alterations of renal tubule transport of various substances have only relatively recently been studied. Despite some progress in the genetics and dif-

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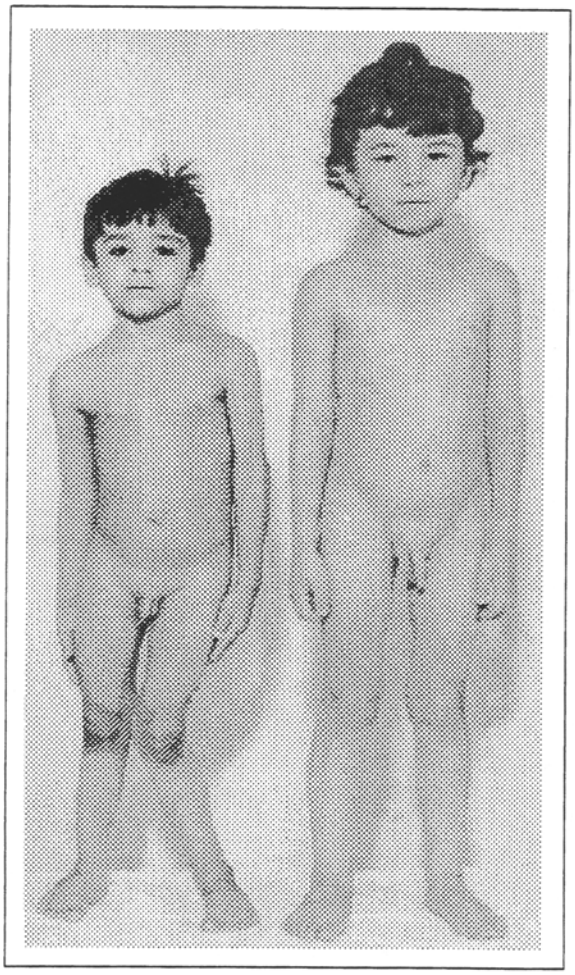

Fig. 1.

ferential diagnosis of these pathological states, many aspects of the pathogenesis and therapy of diseases grouped under the term "tubulopathies" remain unclarified. Without the timely correction of existing abnormalities, tubulopathies progress to the stage of chronic renal failure, which can only be treated by kidney transplantation. However, grafting a health organ in place of a nonfunctioning one is a complicated operation necessitating immunosuppressive therapy for life.

In light of the aforesaid, the attempt to treat membrane transport pathology most likely related to the abolished function of a specific membrane protein by the transplantation not of a whole organ, but of individual cells and tissues, chosen according to the probable pathogenic mechanisms of the given disease, seems of interest.

Emil' S., a boy of five-and-a-half, has been under observation for 1 year 9 months in the nephrology clinic of the Research Institute of Pediatrics, Russian Academy of Medical Sciences.

The family history is troubled: the boy's father suffers from alcoholism and drug abuse. Emil' was the product of a first, normal pregnancy with a body weight of 3200 g and a length of 52 cm. The condition after birth was satisfactory. At an early age he had an acute respiratory viral infection (ARVD), varicella.

A subfebrile state of unclear etiology and retardation in physical development were noted from the infant period on. At the age of 1 year a moderate proteinuria was registered for the first time. Agenesis of the right kidney and dysplasia of the left kidney were found by excretory urography. An elevated level of transaminases was noted in the serum (aspartate aminotransferase to 1603 IU, alanine aminotransferase to 1198 IU). HBs-seropositive hepatitis manifested itself by hepato- (+5 cm) and splenomegaly (+3 cm). He was treated with vitamins, enzymes, hepatotropic drugs, and rheoferon with a positive effect. In September, 1990 (age 2 years 4 months) a transitory rise of the urea level to 48.6 mg% was noted as well as hypocalcemia (1.57 mmol/liter) and glucosuria (0.5%) combined with isostenuria (urine density 1010). In the same period bone changes were

TABLE 1. Laboratory Data before and after THFT in a Child with Fanconi's Syndrome

Index	Date	
	05.93, before THFT	10.93, after THFT
Ca of serum, mmol/liter	2.18 8.72 mg%	2.15 8.6 mg%
Ca of urine, mg/kg/day	7 N 5–6	6.5
P of serum, mmol/liter	1.17 3.63 mg%	1.25 3.9 mg%
P of urine, mg/kg/day	56 N no more than 10–20	22
Aspartate aminotransferase, IU	189.4	61.6
Alanine aminotransferase, IU	205.9	83.7
Urea, mg%	35.4	43.8
Blood creatinine, mg%	1.2	1.4
IgG, mg%	1000	1075
IgA, mg%	55	54
IgM, mg%	70	71
Complement	50	60
T cells, %	41	–
Reaction of blasttransformation of lymphocytes	41	–
CIC	310	325

Note. Here and in Table 2: N – norm.

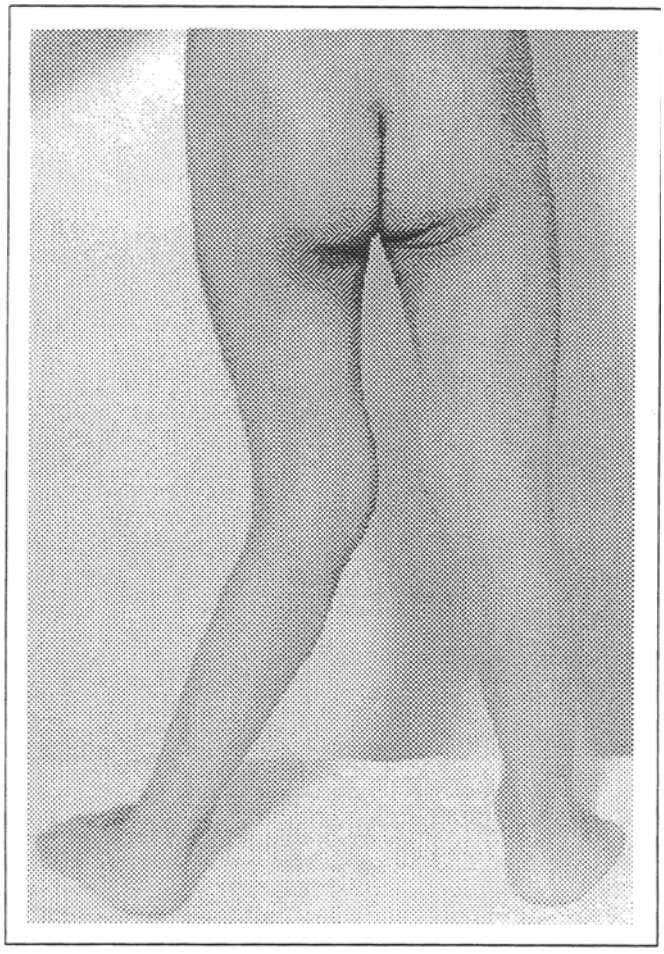

Fig. 2.

noted, namely valgus deformation of the left lower leg and pes planus of the right foot.

He was first admitted to the nephrological department of the Research Institute of Pediatrics in February, 1992, at the age of 4 years. Logoneurosis and delayed physical development (corresponding to 2.5 years) were found (Fig. 1). The boy could not walk by himself. Glucosuria (0.5%), hyperaminoaciduria, hypocalcemia (1.57 mmol/liter), hypercalciuria (11 mg/kg/day), hyperphosphaturia (65.8 mg/kg/day) moderate proteinuria (0.7 g/day), positive HBs antigen, elevated serum transaminases (aspartate aminotransferase - 1603 IU, alanine aminotransferase - 1198 IU), moderate transitory hyperazotemia (48.6 mg%), and roentgenological features of osteoporosis were noted. The clinical diagnosis was: agenesis of the right kidney, hypoplasia of the left kidney; Fanconi's syndrome; chronic HBs seropositive hepatitis in the active stage; pseudohypoaldosteronism; logoneurosis. Therapy with α-calcidol (0.5 μg per day) in combination with calcium carbonate (3 g/day) was begun against the background of therapy of hepatitis (liver diet, vitamin therapy, enzyme hepatotropic drugs). As a result of the therapy the boy began to walk by himself and grew 5 cm in 5 months. Phosphorus and calcium excretion in the urine decreased, and glucosuria disappeared. But frequent (twice a month) ARVD persisted as well as the

TABLE 3. Dynamics of Amino Acid Spectra of Urine Following Transplantation of Human Fetal Tissues

Amino acid	Norm	Before THFT	Five months after THFT
Tryptophan	5–122	149.8	Trace
Tyrosine	5–270	298	Trace
Leucine Trace		8–61	392
Valine	0–85	466	Trace
Phenylalanine	6–188	1026	Trace
Threonine	25–126	1681	417
Serine	67–695	1471	584
Alanine	67–797	2330	1000
Histidine	97–1613	4838	1333
Glutamine	127–681	5065	959
Glutamic acid	27–285	2533	642
Lysine	13–328	1460	416
Glycine	146–1330	1774	1175
Oxyproline		+++free	

TABLE 2. Dynamics of Anthropometric Indexes in a Child with Fanconi's Syndrome

Index	Date of observation				
	9.01.93	11.25.93	02.16.93	05.93	10.93
Age	4.3	4.5	4.7	4.11	5.4
Weight, kg	11 N 17.14±2.18	13.2	13.5	13.9 N 19.7±3.02	16
Height, cm	86 N102.44±4.74	91	94	101 N 110±5.14	
Gain in height		+5	+3	+7	
Size of left kidney, sonography data	68×33 N 70×35			72×34 N 70×40	

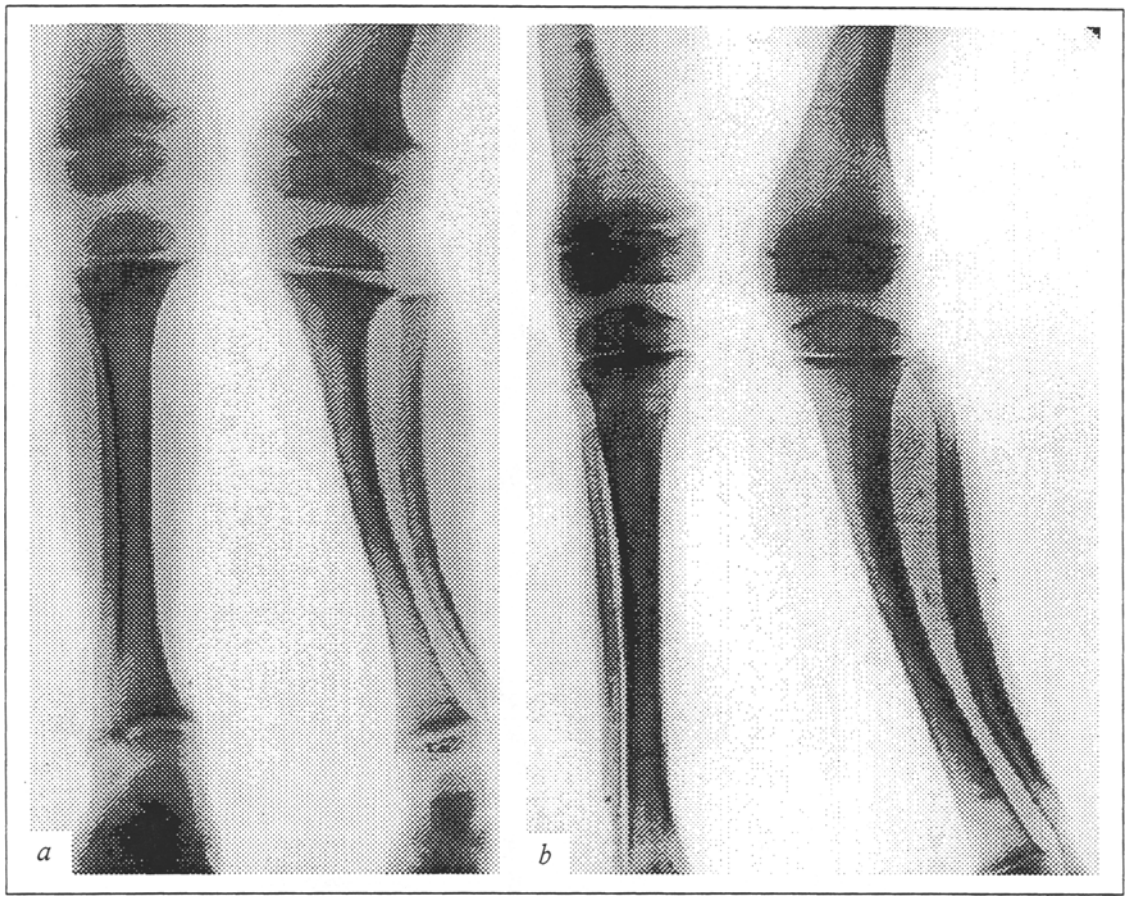

Fig. 3. Angle of deformity of *genu valgum*. *a*) initial x-ray (138°); *b*) final x-ray (153°).

abnormal gait, and bone deformities (Fig. 2); episodes of worsened state (weakness, arterial pressure fall, attacks of nausea and vomiting), appeared in 1992 and were considered manifestations of pseudohypoaldosteronism, HBs antigenemia, the rise of serum transaminases, and hyperaminoaciduria (Tables 1 and 3).

Since the therapeutic effect of the symptomatic therapy mentioned above was terminated, it was decided to perform a transplantation of human fetal tissues (THFT). On May 25, 1993, the patient was given placenta and fetal tissues of liver, cartilage, kidney, and mesenchyme using the method of deep subcutaneous injection.

Five months after THFT the following dynamics of clinical and laboratory manifestations was noted.

The rate of growth increased (the gain in height was 7 cm for 5 months, Table 2). The waddling gait disappeared and valgus deformation of the left lower extremity decreased. The comparison of roentgenograms revealed an increase of the left *genu valgum* angulus from 138 (9.04.92) to 153 (11.29.92). The boy suffered no intercurrent infections after THFT. Enlargement of the left kidney was noted from echographic data. Hypocalcemia and hyperphosphatemia were absent. Hypocalcemia was corrected with the aid of α-calcidol therapy. The level of calcium excretion in the urine practically normalized (Table 1). The degree of hyperaminoaciduria is decreased (Table 3).

To date, logoneurosis is still present, but attacks of pseudohypoaldosteronism are less intense, the hepatolienal syndrome shows a clear decrease of the level of serum transaminases (Table 1), and the height deficit is only 4 cm as compared with the norm. Increased concentrations of circulating immune complexes (CIC) (Table 2) are most likely related to the persistence of HBs seropositive hepatitis.

Thus, the dynamics of the clinical and laboratory manifestations permits one to assume a positive effect of THFT on the course of the disease in this patient. The mechanism of action, however, requires further study.

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