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THYMIC HUMORAL FACTOR (THF) THERAPY IN A PATIENT WITH DI-GEORGE SYNDROME*

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Thymic hypoplasia, or DiGeorge syndrome, is a congenital immunodeficiency characterized clinically by congenital tetany, unusual facies, and increased susceptibility to infection, and pathologically by the absence or hypoplasia of the thymus and parathyroid glands[1-3]. It was first described in 1965 in three patients by DiGeorge[1]. The patients present with a characteristic clinical picture of hypocalcemic tetany in the first days of life, hypertelorism, antimongoloid slant of the eyes, shortened philtrum of the lip, low-set notched ear pinnae and micrognathia. If the patients survive the neonatal period, increased susceptibility to infection occurs, manifested by clinical rhinitis, recurrent pneumonia, otitis media, oral candidiasis and diarrhea. Aortic arch and midline abnormalities are common. There is cellular immunodeficiency and usually normal humoral immunity[4].

The importance of early diagnosis is related to the complete reconstitution of T cell immunity, which can be achieved following a fetal thymus transplant or THF therapy in cases of partial thymic deficiency. This report presents a patient with DiGeorge syndrome treated with thymic humoral factor.

Case Report

BS, a 17-day-old boy, was admitted to Hacettepe Children's Hospital on April 27, 1978, with the complaints of tremor in the hands and convulsions with cyanosis. He was the product of an uncomplicated full-term pregnancy and delivery. His parents were healthy and first cousins. He had two healthy siblings. A brother had died of an unknown illness at the age of seven days.

Physical examination: The patient's weight was 4000 g, height 56 cm, and head circumference 38 cm. His face was characteristic of DiGeorge syndrome with the

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shortness of the philtrum of the lip, mild hypertelorism and low-set, notched ear pinnae and micrognathia (Figures 1, 2). There was overriding of the 2nd, 3rd and 4th toes. There was no cardiac abnormality.

Figure 1

Characteristic facial appearance in the DiGeorge syndrome.

Figure 2

Notched ear pinnae and micrognathia characteristic of the DiGeorge syndrome.

Laboratory examination: Urinalysis was normal. Hemoglobin was 15.60 gm/dl, WBC 8000/mm^3, total lymphocyte count 2800/mm^3. Blood sugar and electrolytes were within normal limits. Serum calcium was 6.9 mg/dl, phosphorus 6.9 mg/dl and alkaline phosphatase 4.2 BU. There was no thymic shadow on the chest radiogram and the aortic arch was on the left. The skin test for phytohemagglutinin (PHA) gave 5 mm induration. His lymphocytes showed no blastogenic response to

$$\text{PHA } \left(\frac{\text{stimulated CPM}}{\text{unstimulated CPM}} = \frac{26}{48}, \quad \text{control's } \frac{6381}{60} \right).$$

He was placed on Vitamin D for his hypoparathyroidism.

At 3 months of age he developed chronic otitis media and bronchopneumonia. He was anergic to skin tests for PHA and candida antigen. In vitro response of the

$$\text{lymphocytes to PHA was low } \left(\text{SI}^{\bullet} = \frac{\text{stimulated CPM}}{\text{unstimulated CPM}} = \frac{21140}{991} = 21.3, \text{ normal}\right.$$

SI $\geqslant$ 20), there was no response to candida and SKSD antigens, but normal response to allogeneic lymphocytes. E rosette was 24% (N: 69 ± 8), EA rosette 38% (N: 12.25 ± 5.56), and EAC rosette 34% (N: 17.75 ± 6.16) (Table I). After incubation with various amounts of thymosin$^{\bullet\bullet}$ (1 to 200 μg per milliliter) his E rosettes showed 59 percent increase. There was no increase in control's rosettes (Table II). The serum immunoglobulin levels (IgG 780 mg/dl, IgM 67 mg/dl, IgA 103 mg/dl, B_1C 92 mg/dl) and the number of lymphocytes bearing membrane immunoglobulins were within normal ranges.

Biopsy of an inguinal lymph node 5 days after stimulation with diphtheria and tetanus toxoid showed the presence of germinal centers and normal plasma cells but mild lymphocyte depletion of the paracortical and deep cortical areas.

The serum thymic hormone level (kindly assayed by Dr. Alberto Astaldi Jr., Amsterdam) was low (5 p moles/10^7 lymphocytes) compared to age-matched healthy controls (N $\geqslant$ 20 p moles/10^7 lymphocytes). There were some target cells among the peripheral lymphocytes.

All the above findings were indicative of DiGeorge syndrome. Because of an increase in T cell rosettes following incubation with thymosin, the patient was

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$^{\bullet}$ SI = stimulation index.

$^{\bullet\bullet}$ Thymosin fraction V kindly donated by Dr. A. L. Goldstein, University of Texas, Galveston.

treated with doses of Thymic Humoral Factor* 1 mm/kg/day intramuscularly five days a week[5]. A total of 55 doses (7.5 mg) of the THF were administered. The patient improved clinically and began to gain weight. He experienced two episodes of gastroenteritis and urinary tract infections which were controlled with antibiotics.

Immunological tests were repeated at the end of the three-month THF therapy: PHA skin test was positive, but skin test for candida remained negative. In vitro response of lymphocytes to PHA showed a marked increase

$$(SI = \frac{\text{stimulated CPM}}{\text{unstimulated CPM}} = \frac{10789}{82} = 131.6),$$

but there was no response to other antigens, namely candida and SKSD. E rosette values showed a greater than two-fold increase following treatment with THF (patient 52%, control 78%, Table I).

TABLE I

LYMPHOCYTE SUBPOPULATIONS BEFORE AND AFTER THF THERAPY

	Patient (rosette %)			Control (rosette %)		
	E	EA	EAC	E	EA	EAC
Before THF	24	38	34	64	8	14
After THF	52	24	29	78	14	18

TABLE II

IN VITRO EFFECT OF THYMOSIN ON E ROSETTE

	Patient E rosette %	Control E rosette %
Without thymosin	24	65
Thymosin 200 μg/ml	51	63
Thymosin 100 μg/ml	43	68
Thymosin 10 μg/ml	40	63
Thymosin 1 μg/ml	42	62

Discussion

DiGeorge syndrome is a rare immunodeficiency disorder which can be diagnosed by typical facial appearance, hypocalcemic seizures and symptoms of congenital heart disease[1-3]. With one known exception of a familial case[6], it occurs sporadically.

Patients who survive the immediate neonatal period may develop recurrent or chronic infections due to viral, bacterial, fungal or protozoal agents. Pneumonia,

* Kindly donated by Prof. N. Trainin, Rehovot, Israel.

chronic infection of the mucous membranes with candida, diarrhea and failure to thrive may be observed.

Our patient had the typical clinical features and laboratory findings along with recurrent infections. He had normal immunoglobulins and normal antibody response. The cell-mediated immunity was found to be defective by various laboratory parameters, including negative skin tests, low E rosettes, low in vitro response of lymphocytes to PHA and antigens, and low level of circulating thymic hormone.

A total aplasia of the thymus and parathyroid glands is not compatible with long survival. Many of these patients have hypoplasia of the thymus and show spontaneous improvement of cell-mediated immunity as they get older if they have not died of congenital heart disease or an overwhelming infection beforehand. Such patients are considered to have partial DiGeorge syndrome.

Various methods have been used in treating patients with DiGeorge syndrome. There are reported cases of the restoration of cell-mediated immunity following fetal thymus transplant[7-9]. Some investigators attempted implantation of fetal thymus in millipore diffusion chambers so as to avoid the risk of graft-versus-host reaction (GVH disease)[6,10]. Transfer factor, thymosin, and recently implantation of cultured thymic epithelium are the other therapeutic methods applied[11]. We selected THF because of our patient's in vitro response to thymosin. After the treatment with THF our patient showed some clinical improvement as indicated by weight gain and the overcoming of respiratory infections, gastroenteritis and measles without complication. Improvement in the patient's cellular immunity was also illustrated by different parameters (E rosettes, in vitro lymphocyte blastic transformation, delayed hypersensitivity reaction to PHA).

The basic immunologic defect of patients with DiGeorge syndrome is not clearly known. Some patients exhibit low circulating thymic hormone levels and target cell response, and others may have low thymic hormone levels without target cell response[12,13]. The first group may show in vitro and in vivo response to thymic hormone therapy. The patients in the second group do not respond to the treatment with thymic hormone, suggesting a defect at the stem cell level[14].

Given our patient's response to THF, we believe him to belong to the first group, classified as partial DiGeorge syndrome.

Summary

The case of a 17-day-old boy, diagnosed as having DiGeorge syndrome with hypoparathyroidism, typical facial features, cell-mediated immune deficiency, normal levels of serum immunoglobulins, normal antibody response and low level of circulating thymic hormone, is presented. After treatment with 55 doses of THF, the patient showed clinical improvement with in vitro and in vivo correction of the tests for cell-mediated immunity.

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