Pathogenetic Role of Dysbacteriosis in the Development of Complications of Type 1 Diabetes Mellitus in Children

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A relationship between enteric microbiocenosis and severity of type 1 diabetes mellitus was detected. Microbiological analysis showed II-IV degree dysbacteriosis in all diabetic children. Long-term therapy with probiotics aimed at eradication of opportunistic microflora resulted in recovery of microbiocenosis, which was paralleled by improvement of the clinical status, regression of complications in children who were ill for a long time, and prevention of complications in children with newly detected diabetes. These results indicate the leading role of chronic enteric toxic infectious process in the development of complications of type 1 diabetes. The significance of infection in the pathogenesis of other noninfectious diseases in man is discussed.

Key Words: *type 1 diabetes mellitus; complications; dysbacteriosis; probiotics*

Co-existence of the host with microflora of its natural cavities is an important biomedical problem. It is now clear that in order to survive, the microorganism should be capable of exerting a potent effect on the host. This thesis is best of all illustrated by the nonspecific mechanisms of reversible destruction of the immune system by viruses. These mechanisms include effects on cell division processes, suppression of apoptosis, synthesis of the complement cascade proteins, histocompatibility antigens, interferons, other proinflammatory cytokins, stimulation of synthesis of interferon- and immunoglobulin-binding proteins, suppressive steroids, *etc.* [6]. In contrast to viruses, the suppressive potential of opportunistic microflora, specifically enteric dysbacteriosis, is little studied. This is explained by impossibility of creating experimental models of bacterial associations and absence of methods for evaluation of integral toxic infectious effects of enteric dysbacteriosis on the host. That is why clinical observations remain the only method for investigation of medical and biological aspects of this important problem. Extremely important data on the relationship of dysbiotic shifts of enteric microbiocenosis and chronic transformation of the pathological process [1,2] were obtained in clinical studies. This suggests an important role of infectious agents in the pathogenesis of atherosclerosis [3], thyroiditis [7], and other diseases traditionally referred to noninfectious.

We investigated the role of enteric microbiocenosis in the pathogenesis of diabetes.

MATERIALS AND METHODS

Thirty-eight patients with type 1 diabetes mellitus (DM1) aged 3-19 years were observed. The patients were examined every 3 months. Clinical examinations, evaluations of glycemic profiles, measurements of glycated hemoglobin, biochemical analysis of the blood, and analysis of feces for dysbacteriosis were carried out. Every 6 months the patients were examined by ophthalmologist and neuropathologist in order to control the development of complications.

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DM1 was first detected in 14 children, 24 children suffered from the disease for more than 1 year. In the group with disease duration longer than 1 year, the disease ran a labile course with liability to hyperglycemia in 70%, to hypoglycemia in 20%, and low exercise tolerance in 40%. Mauriac syndrome was detected in 20% children, redistribution of subcutaneous fat on the chest and abdomen was detected in 60% cases. Late complications of DM1 included cataract, retinopathy, polyneuropathy, nephropathy, cheiropathy, lipodystrophy (lipomas at sites of insulin injections), and hepatomegalia. The disease ran a severe course, with poor insulin tolerance and frequent decompensation.

Patients with newly detected DM1 often complained of general weakness; 78.5% were liable to hypoglycemic states. Physical and sexual development was delayed in 21.4% patients.

Symptoms of intoxication of different severity were initially present in all children: paleness, dryness of the skin, cyanotic haloa round eyes, icteric coloring of palms, subicteric sclera, angular stomatitis.

Dysbacteriosis was corrected with bifido- and lactobacteria-containing dietetic products (biofilin, bifiton, fibilac, bifilux, acidophiline) in daily doses of 10 ml (10^9-10^{10} CFU)/kg during the main course and 4-5 ml/kg during the maintenance course. The duration of the main course depended on the rate of symptom regression. The patients received maintenance probiotic therapy over the entire period of observation (1-8 years). Other agents for microbiocenosis correction included bacteriophages, fungicidal drugs in doses fit for age, digestive enzymes, and food additives [4].

RESULTS

Dysbiotic shifts in all children with DM1 manifested by a drastic increase in the number of some opportunistic bacteria (lactose-negative enterobacteria, *Klebsiella*, enterococci, *Candida*, *Clostridia*, *Staphylococcus epidermidis*, *etc.*) and a decrease or absence of bifido- and lactobacteria, *E. coli* with normal enzymatic activity, and massive growth of two or more opportunistic microorganisms with aggressive factors.

Before the start of therapy the severity of dysbiotic shifts in 50% examinees corresponded to III-IV degree dysbacteriosis. After 1 year no pronounced dysbacteriosis was detected (Fig. 1).

Probiotic therapy modulated the course of diabetes in all the patients. Positive changes were observed in different periods, but the order of disappearance of some symptoms of the pathological process was similar: disappearance of intoxication and malabsorption and improvement of patients' well-being and tissue trophics during the first 3 months of therapy, normalization of liver parameters and acceleration of physical development during the next 3 months. Sexual maturing of pubertal children started during the same period; a trend to stabilization of glycemia and glucosuria appeared. As a rule, this manifested by a lesser scattering of glycemia values in the course of 24 h (3.9±0.28 mmol/liter *vs.* 7.85±0.27 mmol/liter at the beginning of therapy, $p \leq 0.01$), but still, the level of glycemia could be higher than 10 mmol/liter and glucosuria more than 1%.

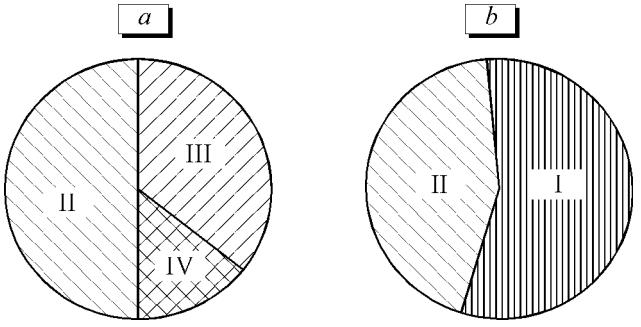

Fig. 1. Structure of dysbacteriosis severity in children with type 1 diabetes mellitus before (*a*) and 1 year after probiotic therapy (*b*). Roman figures: dysbacteriosis degree.

After a year of probiotic therapy, clinical laboratory improvement stabilized. Due to normalization of glycemia, the absolute dose of insulin could be reduced in 26.3% and the relative dose in 52.6% children (from 0.660±0.023 to 0.550±0.017 Units/kg/day, $p<0.05$). Starting from the beginning of therapy, no comas occurred in any of the patients during intercurrent diseases.

Delayed onset of of complications is regarded in modern diabetology as the main criterion of treatment efficiency [5]. In our study none of the children had complications during the entire period of observation (2-8 years). In patients who started therapy with complications they gradually regres-

TABLE 1. Effect of Probiotic Treatment on Time Course of Late Complications of DM1

Complication	Percentage of children	
	before therapy	after therapy
Cataract	23.6	5.2
Retinopathy	41.7	13.1
Polyneuropathy	29.1	10.5
Nephropathy	10.5	0
Cheiropathy	7.8	7.8
Lipodystrophy	83.7	0
Necrobiosis lipoidica	5.2	2.6

sed (Table 1), which was confirmed by instrumental and special examinations.

Approaches to the therapy of children with DM1 from the standpoint of optimizing insulin therapy gave no results. Therapeutic measures carried out at present just ensure patient survival, but do not solve the problem of preventing the disease and its complications. Detection of the pathogenetic role of enteric microbiocenosis in the diabetic process will help to develop a new strategy of DM1 treatment and prevention of nephropathy, polyneuropathy, ophthalmic involvement, and other frequent complications of this disease.

REFERENCES

1. A. V. Valyshev, F. G. Gil'shutdinova, A. A. Tret'yakov, *et al.*, *Zh. Mikrobiol.*, No. 4, 87-88 (1997).
2. A. A. Vorob'ev, L. O. Inozemtseva, Yu. V. Nesvizhskii, *et al.*, *Ibid.*, No. 1, 70-74 (1996).
3. V. G. Likhoded and V. R. Martynov, *Ibid.*, No. 4, Suppl. 117-121 (2000).
4. G. N. Rozanova, D. A. Voevodin, M. F. Logachev, and T. Yu. Shiryaeva, *Sakharnyi Diabet*, No. 2, 34-36 (2000).
5. *Endocrinology* [in Russian], Ed. L. Lavin, Moscow (1999).
6. A. Alcami and Y. Koszinowski, *Immunol. Today*, **21**, No. 9, 447-455 (2000).
7. L. Chiovato, G. Canale, D. Maccherini, and V. Falcone, *Acta Endocrinol.*, **128**, 439-442 (1993).