SECONDARY DIABETES IN CHILDREN WITH THALASSAEMIA MAJOR (HOMOZYGOUS THALASSAEMIA)

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SUMMARY
Life expectancy of patients suffering from homozygous beta-thalassaemia has been improved due to the modern treatment of this disease. This has allowed development of late hemosiderosis-related complications and disturbances of the endocrine and exocrine functions of the pancreas. Carbohydrate metabolism of 16 patients with thalassaemia major was studied. Three of them presented with a pronounced clinical picture and biochemical constellations of a severe diabetes mellitus. The remainder had no clinical symptoms of carbohydrate metabolism disorders. The pancreatic beta-cell function of the patients was assessed by measuring the serum concentrations of immunoreactive insulin and by a glucose tolerance test. Most patients showed very low basal insulin levels while glucose tolerance was reduced in only one of them. In this patient we also established delayed insulin response after an intravenous glucose load. We concluded that the disturbed insulin secretion found in the children studied is most likely the earliest manifestation of the pancreatic beta-cell insufficiency which precedes the changes in the glucose tolerance.

Keywords: diabetes mellitus, thalassaemia major, immunoreactive insulin, glucose tolerance

INTRODUCTION
Optimal blood transfusion in children with homozygous beta-thalassaemia (thalassaemia major) maintaining their haemoglobin level above 115 g/l and performed in conjunction with properly conducted chelating therapy improves these patients' life expectancy. However, it cannot prevent the complications due to secondary hemosiderosis which involves the endocrine system. Iron deposition in the pancreas damages both its exocrine and endocrine functions. The iron accumulates in the beta cells of the islets of Langerhans which results in inadequate secretion of insulin. This is reflected in the impaired glucose tolerance and, in advanced stages, in clinical manifestations of diabetes mellitus.

We followed the course of a pronounced diabetes mellitus in children with thalassaemia major and determined the beta cell activity in children afflicted with the same disease but without clinical evidence of diabetes.

MATERIAL AND METHODS
The present study included a total of 16 patients with thalassaemia major (age 5-20 years) all diagnosed and treated in the Haematology Division of the Children’s...
Clinic in the University of Medicine, Plovdiv. Three of them were with proven diabetes mellitus. The other 13 showed no clinical evidence of carbohydrate metabolism disturbance. The diagnosis of diabetes in the second group of patients was made on clinical and laboratory grounds. Their condition was stable and there were no other causes affecting their carbohydrate metabolism. None of the children had familial predisposition to diabetes. The beta cell function was assessed by radioimmunoassay of the immunoreactive insulin and by an intravenous glucose tolerance test. The basal levels of the immunoreactive insulin was measured in all children. In one of them insulinenia was evaluated dynamically every ten minutes to the sixtieth minute of glucose stimulation. The infusion of glucose was performed intravenously to avoid malabsorption which, due to the liver damage, is always present in such patients. The blood sugar level during the intravenous glucose tolerance test was assessed using the glucose absorption coefficient (k). The clinical and haematologic data on these patients are shown in Table 1.

RESULTS

The course of the clinically manifested diabetes is illustrated by the following three cases:

Case 1. T.D.D., a 16-year-old girl (Reg. No 1755/11.09.1990) with proven homozygous beta thalassaemia since the age of one year. The patient underwent splenectomy at 4. Subsittive blood transfusion treatment and occasional chelating therapy were performed. Secondary hemosiderosis and severe myocardial dysfunction were proven in her from the age of 7 - 8 years. The patient was last hospitalized on the basis of anamnestic and clinical evidence of diabetes mellitus - polyuria, polydipsia, acetonuria, hyperglycemia, and glucosuria. The status revealed the characteristic signs of the underlying disease - characteristic face, haemic infanlilism, hepto- and cardiomegaly. The blood and urine sugar profiles confirmed the suspicion for secondary diabetes mellitus: 07.00 - 18.4

Table 1

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<th>Sex</th>
<th>Years</th>
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<th>Height cm</th>
<th>Hb g/l</th>
<th>k</th>
<th>IRI</th>
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k - coefficient of glucose absorption  
IRI - immunoreactive insulin
Case 3. A.G.S. (Reg. No 22871 14.11.1981). A 16-year-old girl with diagnosed homozygous beta-thalassaemia from the age of 10 months. Splenectomy was performed at four years of age. Since 1987 the child has been placed on hypertransfusion regimen with erythrocytes infusion at Hb < 100 g/l and subcutaneous application of Desferal using infusion pump. Secondary hemosiderosis was present prior to that affecting considerably the cardiac muscle which was confirmed by ECG, echocardiographic and roentgenologic studies. Two weeks before hospitalisation the patient developed polyuria, polydipsia, glucosuria and polyphagia. The clinical status of the patient indicated regular physical and neuropsychic development, and delayed puberty. Hb - 122 g/l, Er - 4.2 x 10^9/l, haematoctrit - 0.38, ESR - 15 mm, thrombocytes - 693 x 10^9. Blood sugar profile - 07.00 - 11.0 mmoll, 10.00 - 16.0 mmoll, 12.00 - 11.4 mmoll, 16.00 - 9.5 mmoll, 19.00 - 10.8 mmoll, 22.00 - 14.6 mmoll. The sugar lost through urine was minimal. Our diagnose was a secondary diabetes mellitus not correctable by the applied diet therapy. The patient was started on insulin therapy (0.25 U/kg b.w) for 24 hours. During the succeeding 6-month follow-up the general condition of the patient remained satisfactory. She achieved clinical and chemical compensation with insulin 6 U in the morning and 4 U in the evening.

Table 1 comprises the biologic parameters of the nontoxic children. The results from the immunoreactive insulin test and the coefficient of glucose absorption during glucose loading of these patients are given in Table 1 and Fig. 1. The immunoreactive insulin had very low values in all investigated subjects. The coefficient of glucose absorption was normal with the exception of one of the children suspected for impaired glucose tolerance (K = 1.2).
Figure 1
Intravenous glucose tolerance test in patients with thalassemia major

Figure 2
Glucose and insulin in a patient with thalassemia major after intravenous glucose tolerance test
The glycemic and insulinemic curves of the patient along with the dynamically followed immunoreactive insulin, stimulated with glucose, are given in Fig. 2. Significant increase of the insulinemia (up to 4 times) was established at the 40th minute after the intravenous glucose, while normal values were reached only at the 60th minute.

**DISCUSSION**

Diabetes in the different pathologic processes including secondary hemosiderosis is usually described as a disorder having a mild course and no tendency towards ketoacidosis and spontaneous remissions. Insulin needs are either very small or none. There is seldom diabetic microangiopathy. The clinical picture in the three patients we treated started with the classical symptoms of the disease and followed a severe course. Ketoacidosis was present in two of them which was coped with only after administration of insulin. In one of the children there was evidence of diabetic nephropathy and capillaropathy. The course of the underlying disease with severe complications present in the cardiovascular and excretory systems determined the unfavourable progression of the diabetes and the lethal outcome in two of the patients. In the third diabetic patient the carbohydrate metabolism compensated after administration of small doses of insulin. She received a relatively adequate iron chelation therapy during the last four years while such therapy was performed only occasionally in the other two patients. There was marked hemosiderosis with high serum levels of iron and ferritin in the three patients who were over 16 years old.

The second group of thalassaemic children had normal glucose tolerance except for one of them in whom the coefficient of glucose absorption had borderline values raising suspicions of decreased glucose tolerance. The most accurate method of determination of the insulin serum concentration indicating the functional activity of the pancreatic beta-cells is the method of radioimmunoassay. Although the basal levels of insulin bear a small informative value for the diagnosis of diabetes mellitus, a study of the insulin secretion dynamically, after glucose stimulation, is of major importance in the detection of preclinical forms of diabetes which are still devoid of glucose tolerance abnormalities. Insulin secretion decreases during the earliest phases of diabetes. In direct stimulation by intravenous glucose tolerance test the deviations in the insulin secretion are more pronounced and can be detected considerably earlier than glycemia.

The basal insulin secretion in our patients was either absent or in a very low concentration. However, without studying it dynamically we could not have made any conclusions for the presence of stable insulinemia in the investigated children. During the intravenous glucose load of patients with normal carbohydrate tolerance we observed a rapid and sudden eight-fold increase of insulinemia - as early as the first 10 minutes. This was not observed in the diabetic patient in whom we investigated the insulin levels in the course of the intravenous glucose load. The delayed insulinemic response to the glucose stimulation showed lower than normal levels of insulin. This indicated torpid insulin secretion, characteristic of the earliest stages of diabetes. Normal blood sugar curve in the same child is common for this stage of the disease. The delayed insulin response is assumed to be the result of abnormalities in the carbohydrate tolerance which cannot be detected by glucose loading. The conclusion based on these results is that in the studied thalassaemic children whose diabetes was not clinically manifested it was the insulin secretion that was most probably disturbed and this could be the earliest manifestation of insufficiency of the beta-
cell of the pancreas.
In conclusion, by prolonging the life of
thalassaemic patients opportunities are cre-
ated for diabetes mellitus to develop. This
fact necessitates early detection and timely
treatment of the complications of the car-
bohydrate tolerance in these patients.

ВТОРИЧНЫЙ ДИАБЕТ У ДЕТЕЙ С
ГОМОЗИГТОЙ ТАЛАССЕМИЕЙ
(ТАЛАССЕМИЯ МАJOR)

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И. Иванов

РЕЗЮМЕ
Современное лечение гомозиготной тала-
семии увеличивает продолжительность
жизни больных этим заболеванием. Соз-
далось возможность обнаруживать поздно
являющиеся осложнения, связанные с
гепатоцитами, включая также и с нару-
шениями в эндокринной и экзокринной
функциях поджелудочной железы. Исследо-
ван углеводный обмен 16 пациентов с
thalassaemia major в возрасте от 5 до 20 лет.
У трех из них наблюдалось выраженная клини-
ческая картина и биохимические показатели
тяжело протекающего сахарного диабета.
У остальных 13 пациентов отсутствуют
клинические симптомы нарушения в углево-
дном обмене. У них авторы определили
функциональное состояние панкреатической
β-клетки, исследуя сократительные концент-
рации иммунореактивного инсулина и
глюкозную толерантность. У больного
обследуемых наблюдали уровни инсулина очень
низкие, в то время как глюкозная толеран-
тность уменьшена только у одного из
них. При венозном обмене глюкозы у
этих пациентов наблюдается запаздывавший
инсулиновый ответ. Авторы пришли к вы-
воду, что у обследуемых детей нарушение
инсулиновой секреции нередко всего пред-
ставляет собой раннее проявление неде-
статочностью β-клеток панкреаса, пред-
шествующей изменениям в глюкозной толе-
рантности.

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