CONTENTS

S. Kostianev, D. Ilchev
Clinical Evaluation of the Elos Pneumostachograph

S. Kostianev
A New Approach to the Evaluation of Bronchodilator Response

E. Karahanyan, B. Biskinov, M. Pechikova, D. Grozeva,
Z. Mantarkova, N. Chalakova, E. Teodosieva, I. Ivanov:
Degenerative Vascular Changes in Children with Diabetes Mellitus

N. Chalakova-Atanasova, V. Daskova, T. Vassileva
Clinical and Electrophysiologic Study of the Brain and
Peripheral Nerves Disorders in Chronic Alcoholism

G. Hatzigeorgiev
Computed Tomographic Bioconstants of the Uterine Cervix

A. Popova
Locomotor Rating of Young Men Investigated in a
Clinical Kinesiologic Screening

G. Balladjiev
Ultrastructural Features in the Structure of Blood
Capillaries of the Haverson Canal

Y. Kousmichev, S. Petkov, V. Kalchev, G. Gozmanov
Diagnosis and Treatment of Traumatic Intracranial
Hematomas and Hydromas According to the Hospital Type

Y. Kousmichev, S. Petkov, G. Gozmanov
Case of Delayed Subdural Hematoma

S. Goranov, I. Hristova, K. Pencheva
Nephrogenic Diabetes Insipidus - Prodomal Phase of
Multiple Myeloma

"Collection of Research Works" -
International Edition of Plovdiv
University of Medicine, Bulgaria

EDITORIAL BOARD

Prof. P. Sotakov - Editor-in-chief
Prof. D. Ilchev - Secretary
Prof. A. Atanasov - Science Editor

Members: Prof. N. Atanasov,
Prof. K. Atanasov, Prof. T. Piperkov,
Prof. D. Mitkov, Prof. E. Karamyan,
Prof. J. Lukanov, Prof. P. Mirov,
Ass. Prof. N. Chalakova-Atanasova,
Ass. Prof. I. Dimitrov

Published quarterly and distributed by
University of Medicine, 15 A Vasil Apriliev St., 4000 Plovdiv, Bulgaria

Editorial correspondence to
The Editor
FOLIA MEDICA,
University of Medicine,
15 A Vasil Apriliev St.,
4000 Plovdiv, Bulgaria
Telephone (02) 443 839

Typset by UM-Centre for educational
and scientific materials, Plovdiv
Printed in Bulgaria by Polygraphia,
Plovdiv.
Translated by Ognyan Obretenov
Editor of Bulgarian text - Maria Popova
Editor of English text - George Davis
Technical editor - Ognyan Obretenov
Proof-reader - Ognyan Obretenov
DEGENERATIVE VASCULAR CHANGES IN CHILDREN WITH DIABETES MELLITUS

E. Karahanyan¹, B. Boikinov¹, M. Pechilkova¹, D. Grozeva¹, Z. Mantarkova¹, N. Chalakova², E. Teodosieva², I. Ivanov¹
¹Department of Paediatrics, ²Department of Neurology, ³Department of Dermatology. University of Medicine, Plovdiv

SUMMARY
Twenty three diabetic children aged 4 to 16 years with duration of the disease from 2 months to 10 years were investigated for microvascular complications. Eight of them (34.8%) had kidney disorders (low creatinine clearance, fluctuating microproteinuria, echographic changes), and nine children (39.1%) had peripheral neuropathy (sensory disorders as assessed by electromyography). Seven children (30.4%) were found to have microscopic alterations of the capillary loops of the nail wall. Ophthalmopathy was found in two (8.7%). There was no correlation between the microvascular complications and the age of children. The duration of the disease affected the severity of the complications. Microangiopathy was related to the degree of compensation of diabetes.

It is emphasized in conclusion that the degenerative vascular complications have their onset rather early in childhood diabetes. They can be detected simultaneously with the diagnosis of diabetes, and therefore should be sought, duly diagnosed and treated.

Key words: diabetes mellitus, nephropathy, neuropathy, ophthalmopathy, capillarscopy

INTRODUCTION
Several years after insulin had been included in the therapy of diabetes mellitus it became evident that diabetic patients ran the risk of developing a number of metabolic and vascular complications. Today, diabetic coma is no more a death-causing factor for diabetics. The degenerative vascular syndrome which manifests itself as both micro- and macroangiopathy and affects almost every system in the body is the major problem at present. The severity and course of diabetes mellitus in children depend to a large extent upon the development of vascular complications. During childhood the microcirculation of the eyes, kidneys and the nervous system are affected much more frequently and more severely than are the large vessels. Such involvement proves to be of great importance for the diabetic children later in their life. Early detection of the microangiopathy has a great practical significance especially in the juvenile insulin dependent diabetes. Detection

Correspondence and reprint request to: E. Karahanyan, University of Medicine, Department of Paediatrics
15A Vasil Aprilov St., 4000 Plovdiv, Bulgaria
Received 30 June 1993; Accepted for publication 14 October 1993
of alterations in the small vessels during the initial stage and their timely treatment usually arrests further progression or even leads to disappearance of these lesions.

The aim of our study was to achieve early diagnoses of the microvascular complications in a contingent of children with diabetes mellitus monitored by us.

**MATERIALS AND METHODS**

Twenty-three patients with insulin-dependent diabetes mellitus aged 4 to 16 years were entered into the study - eight children less than 10 years old and 15 children less than 16 years old. They were assigned to three groups according to the duration of the disease: up to one year - 13 children, from 1 to 5 years - 8 children and from 5 to 10 years - 2 children.

Instrumental and biochemical methods of investigation by which the functional state of the small vessels can be assessed were used for early diagnosis of microangiopathy. Renal function was estimated by measuring proteinuria (according to the method of Kanin), and endogenous creatinine clearance as well as by ultrasound study of the kidneys. Electromyography of the upper and lower limbs was used in searching for peripheral neuropathy. Eyes’ fundi were assessed by fundoscopy, and, for some of the patients, by biomicroscopy. Capillaroscopy of the nail wall was performed with stereomicroscope.

Liver lipid and protein metabolism biochemical markers were measured in all children.

The degree of compensation at the time of investigation was assessed on the basis of blood sugar and urine profiles and the glycosylated haemoglobin level. Chemical compensation was found in nine, clinical compensation in ten and decompensation in four children. Correlation was sought between the detected microvascular complications and the children’s age, the duration of the disease, and the degree of carbohydrate metabolism compensation.

**RESULTS**

Of the 23 children studied, eight (34.8%) had no complications. Changes in one or several systems were detected in the remaining 15 children (65.2%) (Fig. 1 and Table 1).

The percentage of children with complications of the peripheral nervous system was the highest (nine children, 39.1%). These complications were predominantly asymptomatic, only two children complained of weakness and tingling in their extremities. Most of the electromyography results indi-

<table>
<thead>
<tr>
<th>Distribution by localisation</th>
<th>Total number n = 23</th>
<th>Frequency of the complications by age, yrs</th>
<th>Frequency of the complications by duration, yrs</th>
<th>Type of compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4 - 10</td>
<td>11 - 16</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Nervous system</td>
<td>9</td>
<td>2</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Kidneys</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Skin</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Eyes</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n = 8</td>
<td>n = 15</td>
<td>n = 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35.7%</td>
<td>46.1%</td>
<td>62.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33.3%</td>
<td>12%</td>
<td>50.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.5%</td>
<td>50.0%</td>
<td>50.0%</td>
</tr>
</tbody>
</table>
cated decreased sensory conduction of the lower extremities. The upper extremities were also affected in two of the children. These complications were found in the early stages of the disease. The diabetes was newly diagnosed in four patients. The complications in the urogenital system were next in frequency. They were found in eight children (34.8%) and had an asymptomatic course. Hypertension and lipid and protein profile abnormalities were absent. There was a mild and fluctuating proteinuria, most often assessed as opalescence according to method of Kenan, and disturbed glomerular filtration. The clearance of endogenous creatinine was repeatedly measured. It was found to be high in two and decreased in the rest of the children. The ultrasound study of the kidneys in two children revealed slight hydronephrosis caused most probably by the polyuria in them. None of the children were found to have familial predisposition to cardiovascular diseases and disorders of the urogenital system.

The stereomicroscopy of the capillaries of the nail wall revealed various lesions of the vessels in 7 children (30.4%) ranging from small apical dilation to deformation of the capillary loops. One of the children with a ten-year history of diabetes had deformations of the capillaries with single aneurysms and thrombosis.

Eye fundi pathology such as enhanced light reflex of the arterial vessels and microhaemorrhages were found only in two of the children (8.7%) with a 10-year history of diabetes.

Simultaneous changes in the urogenital and the nervous systems and in the skin and eyes were found in nine of the patients (39.1%).

The distribution of microangiopathies by age groups shows that they have higher frequency (not statistically significant; P > 0.05) in older children (Fig. 2). Seven of the 15 children with microvascular changes had initial diabetes with duration of the disease from several months to one year. This suggests that the disease duration in the patients we studied had no effect on the prevalence of complications (P > 0.05; Fig. 3). However, studying the severity of the complications we found that they correlated with the duration of the illness. Both of the children with diabetic ophthalmopathy accompanied by renal and dermatovascular pathology had a 10-year history of diabetes.

The correlation between the prevalence of microvascular complications and the level of compensation of diabetes is presented in Fig. 4. There was a statistically significant difference between the percentages of microvascular pathology in the children with chemically compensated and decompensated diabetes (P < 0.01). All the children in the latter group inevitably suffered from microvascular changes.

Figure 1
Frequency of microvascular complications

- Without complications
- With complications
Figure 2
Distribution of the children by age groups.

Figure 3
Distribution of the children by degree of compensation of diabetes.

Figure 4
Distribution of the children by duration of diabetes.
DISCUSSION

Even when properly treated, the insulin-dependent diabetes is accompanied by severe vascular complications. Histological examinations show generalized diabetes-specific thickening of the basal membranes of capillaries and arterioles, PAS-positive glycoproteins and neutral mucopolysaccharides deposited in their walls as well as proliferation of the endothelium. The genesis of this microvascular syndrome is not yet fully elucidated. There is much evidence implicating hyperglycaemia, hyperinsulinemia, and inadequate fat-rich diet as etiologic factors. Hyperglycaemia causes an abnormal protein glycosylation and progressive deficiency of tissue perfusion as a result of the vascular atherosclerosis. It also activates the polyol pathway followed by sorbitol and fructose accumulation in the eye lens, kidneys, in the peripheral nervous system and in other organs which use this pathway for glucose utilization. Other factors such as genetic (HLA-haplotype), hormonal (mainly the growth hormone), immunologic (presence of antibodies), haemorrhheologic (hyperfibrinogenemia, aggregation of thrombocytes, etc.) are engaged in the genesis of this microvascular syndrome.

Diabetic nephropathy is the major cause of increased mortality rate in type 1 diabetes mellitus. The risk of renal complications is greater in diabetes that manifests itself in early age. The onset of the nephropathy is very difficult to detect. Its manifestation occur slowly and unnoticeably. There are no specific symptoms. The only early indicator is the presence of microalbuminuria. It was observed in 12 to 20 % of the diabetic children.

Increase of the vascular wall permeability for proteins has been observed in childhood diabetes mellitus. Microcirculation alterations occur earlier than the overt morphologic changes. Increased glomerular filtration and enlargement of the kidneys with deposition of various proteins in the mesangium are the result of the increased glomerular capillary permeability to macromolecules. Glomerular filtration in diabetic patients increases considerably in the early stages of the disease in comparison with that in age and sex matched healthy children. The significance of the kidney size in early diagnosis of nephropathy assessed by ultrasound study is pointed out by Bl Abdilaev et al. A. Drash et al. think that detection of the hyperfiltration, nephromegaly and microalbuminuria in the preclinical stage of nephropathy affords opportunities for early treatment and delay of further progression of the changes. Intermittent proteinuria and abnormal creatinine clearance were the early discrete manifestations of renal microangiopathy that we found in 34.8 % of the children we studied.

The frequency of diabetic neuropathy is not precisely determined because of the different diagnostic methods used for its investigation. The generally accepted approximate frequency is 40 % and it was confirmed by our study. This complication does not correlate with the diabetes duration. Its most frequent type is diabetic polyneuropathy. The lower extremities are affected more often than the upper ones. The sensory symptoms are the earliest and the most common manifestation. Motor symptoms may sometimes appear later on in the advanced stages. Electromyography allowed us to detect early, prior to the clinical manifestation, presence of initial manifestation of neuropathy in 39.1 % of the patients.

The changes in the microcirculation in 30.4 % of the patients were confirmed by microscopy of the capillary loops of the nail wall. The ability to use capillaroscopy to detect microvascular changes in the early stages of childhood diabetes was described by J.M. Mouton et al. M. Von Cislo et al. found microangiopathy in 17 out of 20 children with compensated diabetes using electron microscopy of skin blood vessels.
Some of them had only a several months course of clinically manifested illness.

Ophthalmic complications usually appear after the first several years of diabetes. Cerutti et al. (cited by 7) reported a period of at least 6.6 ± 3.0 years between the onset of the disease and the first alteration of the retina. His conclusions are consistent with our findings in the two children with a 10-year history of diabetes. We think, however, that the application of more precise diagnostic methods, such as fluorescent angiography, would have helped us to make the early diagnosis of diabetic retinopathy more precise.

The frequency and severity of vascular complications in diabetes are most often related to the age of onset, the duration of the disease and the metabolic control.

An increased risk of complications in cases with onset of diabetes at an early age has been reported. In our study we did not find any correlation between the age of onset and the presence of complications.

It is well known that microvascular complications are directly correlated with the duration of diabetes. This parameter is assumed by a great number of researchers to be the major risk factor for the development of vascular damage. The first clinical symptoms are thought to occur as early as five years after diabetes has been diagnosed. Application of more precise diagnostic methods recently, however, revealed the existence of vascular complications in a large number of children immediately after the disease was diagnosed. CL, Menibus et al. 6, Kniazev et al. 8, D. Hilt 10 found first symptoms of microangiopathy in 20 out of 75 newly diagnosed diabetic children, a finding which related to the rapidly advancing changes in the cellular membranes following the development of the insulin deficiency. In the authors' opinion, the microcirculatory pathology in these cases depends on the genetic features of the vascular structure and the metabolic disorders. In our study, microangiopathy was manifested in 53.8% of the newly diagnosed diabetic children with duration of the disease of up to one year.

The dependence of these complications on the level of compensation of diabetes described in several papers 19,21,22 was confirmed in our children, too.

CONCLUSION

Diabetic microangiopathy is a complication that starts simultaneously with the clinical manifestation of diabetes. It should be sought, therefore, very early, even during the initial stage of the disease while the changes have not yet become irreversible. Application of modern diagnostic methods, proper treatment and, most importantly, constant glycemic control would lead to considerable improvement of the severe microvascular complications in children.

REFERENCES

СОСУДИСТОДЕГЕНЕРАТИВНЫЕ ИЗМЕНЕНИЯ У ДЕТЕЙ, БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ

Е. Караканян, Б. Бойкянов, М. Печилова, Д. Грозданов, З. Мантаркова, Н. Чалыкова, Е. Теодосиева, Н. Иванов

РЕЗЮМЕ

Предметом настоящей работы являются микроваскулярные осложнения у 23 детей в возрасте от 4 до 16 лет, больных сахарным диабетом. Давность заболевания от 2 месяцев до 10 лет. У 8 детей (34,8 %) выявлены почечные нарушения (повышенная креатининовая клиренс, отчетливые изменения микроскопии мочи, хронофографические нарушения), у 9 детей (39,1 %) — периферические невропатии (электромиография говорит о сенсорных нарушениях), реже — у 7 детей (30,4 %) наблюдаются микроскопические изменения капиллярных петель почечного валика, а у 2 детей (8,7 %) наличие спирального сужения. Зависимость между микроваскулярными изменениями и возрастом детей не установлена. Давность заболевания оказывает влияние на тяжесть осложнений. Появление микроангиопатии связано со степенью компенсации диабета. В заключение авторы подчеркивают, что сосудистодегенеративные осложнения при диабете в детском возрасте проявляются сложившимся ранее. Их можно установить еще при обнаружении диабета. Вот почему их следует искать, вовремя диагностировать и лечить.