Consistency of microvascular and autonomic abnormalities in diabetes

F H Karachaliou, K Karavanaki, R Greenwood, H Morgan, J D Baum

Abstract

The progression of early measures of microvascular disease and autonomic neuropathy were studied in a group of 81 children with insulin dependent diabetes mellitus over a mean interval of 4.2 years. Repeated measurements were made of blood pressure, albumin excretion, joint mobility, and pupillary dilatation in darkness. Over the years between the first and the second study, systolic and diastolic blood pressure showed positive tracking correlations ($r = 0.38$ and $r = 0.32$) with a small but significant deviation from normality; albumin/creatinine ratio was significantly increased (0.79 v 0.55); a greater number of children were identified in the second study as having limitation of mobility of the fifth metacarpophalangeal joint; and pupillary dilatation in darkness significantly decreased (61.5% v 62.9%); 62% of the children with one or more abnormal measurements in the first study were found to have measurements outside the normal ranges in the second study, indicating a consistency in observations over time. It remains to be seen with what accuracy these measurements predict adult onset clinical disease.

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Diabetic complications first become clinically apparent during the second and third decades of life. However, microvascular¹⁻⁴ and autonomic^{5,6} abnormalities may be demonstrable in children with relatively short diabetes duration. It is uncertain whether such findings remain consistent in individuals and with what accuracy they predict adult onset clinical disease. Such information is essential if progress is to be made in targeted intervention trials in childhood on the prevention of the complications of diabetes.

We report here a study of a cohort of children with diabetes, a proportion of whom show abnormalities which are consistent over time.

Methods

In 1986, a longitudinal study was initiated to document early markers of microvascular disease and autonomic neuropathy in diabetic children living in the population geographically defined by Avon County, United Kingdom.

Measurements of blood pressure, urinary albumin excretion, and joint mobility were performed on two occasions seven months apart, and groups of children with abnormal measurements on both these occasions were identified (study I). Pupillary dilatation in darkness, as a marker of autonomic dysfunction, was added to study I as part of the second set of measurements; 81 (63%) of the same group of children were reassessed four years later (study II) to evaluate the consistency of findings and identify any children showing persistent abnormalities.

SUBJECTS

Eighty one of the original cohort of 129 diabetic children were reassessed after approximately four years (mean interval 4.2 years, range 3.4-4.8 years). At the time of study I their age ranged from 3.7 to 16.8 years (mean 11.2 years) and duration of diabetes from 0.1 to 12.6 years (mean 3.8 years). Of the 48 who were not reassessed in study II, nine had moved away from Avon and 39 declined to take part. These 48 were older than those who agreed to participate (13.0 v 11.2 years) but did not differ significantly in other characteristics.

Control measurements were obtained from 121 (in study I) and from 65 (in study II) age and sex matched healthy children (the diabetic subjects' best friends).

BLOOD PRESSURE

Blood pressure was measured in the right arm with the child seated, using a random zero sphygmomanometer with the appropriate sized cuff, taking the fifth Korotkoff sound as the diastolic blood pressure. As blood pressure normal ranges are age and sex dependent, results were expressed as a SD score related to the 1987 Task Force on Blood Pressure Control data⁷:

Blood pressure SD score = (blood pressure measurement - mean)/SD, where mean and SD are derived from the normal age and sex matched population.

URINE ALBUMIN EXCRETION

Urinary albumin excretion was measured on overnight urine samples. These were selected in preference to 24 hour or daytime collections because the intraindividual variability has been shown to be minimal.⁸ Urine albumin concentration was measured by the immunoturbidimetric assay (using the Cobas test) with an intra-assay coefficient of variation (CV) of 4%, an interassay CV of 6%, and a sensitivity of 0.5

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Table 1 Data on control children in studies I and II

Variables	Study I (n=121)	Study II (n=65)
Age (years) (mean, SD)	11.9 (3.4)	15.6 (3.6)
Sex	52:69	29:38
Systolic BP SD score (mean, SD)	0.23 (0.8)	0.13 (0.7)
Diastolic BP SD score (mean, SD)	0.23 (0.8)	0.14 (0.7)
Pupil diameter % (mean, SD)	65.2 (4.3)	64.8 (4.0)
ACR (mg/mmol) (geometric mean, 95% tolerance limits)	0.49 (0.15 to 1.60)	0.47 (0.14 to 1.57)

BP = blood pressure; ACR = albumin/creatinine ratio.

mg/l. Urine creatinine was measured by the Jaffe reaction. Urine albumin excretion was expressed as the geometric mean urine albumin/creatinine ratio in mg/mmol of two consecutive overnight urine samples.

JOINT MOBILITY

The prayer sign¹⁰ was used to examine the presence of limited joint mobility. In addition, each child was asked to place both hands down with fingers fanned on a desk top and the ability to appose the fingers to the flat surface was assessed. Children were classified in stages 0-III as follows:

Stage 0: if they were able to make complete approximation;

Stage I: if they were unable to make contact with some portion of a finger of one hand, usually the metacarpophalangeal (MCP) or the proximal interphalangeal (PIP) joint of the fifth finger;

Stage II: if they could not make contact with PIP or MCP joint of the fifth finger of both hands;

Stage III: if two IP joints were affected and/or more than one finger was affected.

Only children in stage II or III were considered as abnormal.

PUPILLARY DILATATION

Each child had the right eye photographed using a Polaroid pupillometer. The apparatus and photographic technique were identical to that described by Smith *et al.*⁹ The pupil and iris diameters were measured from the photograph and the pupil expressed as a percentage of the iris diameter using the formula:

Pupil diameter % (PD%) = (pupil diameter/iris diameter) × 100.

GLYCAEMIC CONTROL

This was assessed by glycated haemoglobin (HbA_{1c}) measurements at every routine clinic visit (every three to four months) over the period of two years preceding each dataset collection.

HbA_{1c} was measured by an electrophoretic method, the normal range being 5.5-7.5%. The same laboratory method was employed for study I and study II.

All the clinical measurements made in study II were made by one observer (FK) 'blind' to the results from study I (made by KK) and only after analysis were the data from the two studies linked together.

STATISTICAL METHODS

Computation and statistical analysis was performed using the SPSS system. Albumin/

Table 2 Characteristics the 81 diabetic children followed up (mean, SD)

Variables	Study I	Study II
Age (years)	11.2 (3.4)	15.4 (3.5)
Sex (M:F)	33:48	33:48
Duration (years)	3.8 (3.2)	8.0 (3.3)
HbA _{1c} (%)	11.1 (2.2)	11.3 (2.0)
Blood glucose (mmol/l)	9.4 (3.7)	9.5 (3.6)
Insulin dose (U/kg/d)	0.80 (0.2)	0.94 (0.3)

creatinine ratio values were logarithmically transformed to ensure normality. The distribution of all other values was found to be normal and conventional parametric statistics were used. Comparison of results between diabetics and controls or between abnormal and normal results of diabetic children were made by use of Student's *t* test. Paired *t* test was used for comparisons of values between the two studies. Associations between variables were examined using Pearson's correlation coefficients and χ^2 analysis. A probability of less than 5% was taken as significant for all tests.

Results

Apart from age, there was no significant difference in the results for the control children between studies I and II (table 1).

The characteristics of the 81 diabetic children examined in both studies are shown in table 2.

Mean (SD) HbA_{1c} concentration in study II was 11.3% (2.0) which was not different from that in study I (11.1%) (mean difference: 0.24; SE: 0.25).

The tracking correlations for systolic and diastolic blood pressure between the first and second study were $r = 0.38$, $p < 0.001$, and $r = 0.32$, $p < 0.01$, respectively (fig 1). Thus

Figure 1 Relation of follow up to initial standardised scores (A) for systolic and (B) for diastolic blood pressure (BP).

Table 3 Measurements of BP, ACR, PD% and LJM of the 81 diabetic children followed up from study I and study II

	Study I	Study II	p Value
Systolic BP SD score (mean, SD)	0.23	0.28	0.67
Diastolic BP SD score (mean, SD)	0.29	0.34	0.71
ACR (mg/mmol) (geometric mean, 95% tolerance limit)	0.55 (0.1 to 2.88)	0.79 (0.09 to 6.48)	< 0.01
No of children with LJM (stage II/III)	7/81	14/81	< 0.05 (McNemar's test)
Pupil diameter % (mean, SD)	62.9 (4.5)	61.5 (4.5)	< 0.001

BP = blood pressure; ACR = albumin/creatinine ratio; LJM = limited joint mobility.

there was a small but significant positive relation between the blood pressure measurements in study II and study I. The standard scores of both systolic and diastolic blood pressure in study II were, however, not significantly different from those in study I (systolic: 0.28 *v* 0.23, mean difference 0.045; SE 0.1; *p* = 0.67; diastolic: 0.34 *v* 0.29, mean difference 0.046; SE 0.11; *p* = 0.71).

Other study II measurements were compared with study I (table 3): the geometric mean (95% confidence interval) for the albumin/creatinine ratio was 0.79 (0.09 to 6.48) mg/mmol, which was significantly greater than that in study I, 0.55 (0.1 to 2.88) mg/mmol (mean difference 0.72; SE 1.14; *p* < 0.01).

The number of children with limited joint mobility in study II was double that in study I (14/81 *v* 7/81, McNemar's test = 5.4, *p* < 0.05).

Pupillary adaptation in darkness in study II was 61.5% (4.5), which was significantly reduced compared with that of study I—62.9% (4.5) (mean difference 1.43; SE 0.24; *p* < 0.001).

There was a close correlation between the measurements of pupillary dilatation in the two studies (*r* = 0.94, *p* < 0.001) (fig 2). The decrease in PD% could not be attributed to age, as PD% was not associated with age in either diabetic or control children in study I or study II. In diabetic children there was a significant negative correlation between PD% and measurements of glycaemic control (*r* = -0.40, *p* < 0.01) and a weaker association between PD% and duration of disease (*r* = -0.25, *p* < 0.05).

Figure 2 Scattergram comparing PD% results between the two studies.

Table 4 Consistency of abnormal measurements

	Children with abnormalities in			
	Neither of the studies	Study I only	Study II only	Both studies
Blood pressure	62	12	7	5
Albumin/creatinine	59	12	10	9
Limited joint mobility	66	7	8	6
Pupillary dilatation %	72	5	4	5

CONSISTENCY OF ABNORMAL MEASUREMENTS

In study I a group of 27 children was identified as having one or more abnormal measurements. In study II, 17 of these 27 children (63%) again showed abnormal values for the same or additional tests (table 4).

Blood pressure

Of the 12 children who had raised blood pressure in two sessions of measurements in study I, five (42%) were found to be above the defined confidence intervals for age and sex in study II. An additional seven children were identified with abnormal blood pressure measurements in study II.

Urine albumin excretion

Of the 12 children with albumin/creatinine ratio values above the normal range on both sessions in study I, nine (75%) were found again above the normal range. An additional 10 children were found to have abnormal values in study II.

Joint mobility

Of seven children identified as having stage II or III of joint limitation in study I, six (86%) and an additional eight children were shown to have joint limitation in study II.

Pupillary dilatation

All five children identified as having abnormal PD% in study I had PD% below the normal range defined from the control group in study II. An additional four children were below the normal values in study II.

COEXISTENCE OF ABNORMALITIES

Previous studies have shown a high rate of concordance between specific diabetic complications.¹¹ The nine children identified in both studies with a raised albumin/creatinine ratio were all more than 15 years old, all had a urine albumin excretion of > 15 µg/min, but none had frank albuminuria (urine albumin excretion > 200 µg/min). One child from study I also had a raised blood pressure. In study II he was also found to have both a raised albumin/creatinine ratio and raised blood pressure. An additional two of the children with a raised albumin/creatinine ratio were found to have raised blood pressure in study II.

In study II both systolic and diastolic blood pressure scores of the group of children with a raised albumin/creatinine ratio were significantly higher than those of the rest of diabetic children, whereas their blood pressure scores in the first study were not different from the rest of diabetic children.

The degree of coexistence of abnormalities noted in study I was more evident in study II, with the number of children with more than one abnormal measurement being significantly greater (15/78 *v* 6/78, McNemar's test = 9, $p < 0.01$).

Thus in study I two children had three abnormalities: one of these had abnormal measurements on all four tests in study II. There were four children in study I with two abnormalities; in study II three of them had an additional abnormal measurement. Another nine children had more than one abnormality in study II.

Discussion

Subclinical changes in renal function,¹⁻³ blood pressure,⁴ and autonomic function^{5,6} in diabetic children have been reported even in early childhood. However, it is uncertain whether these changes are consistent over time and can serve as markers for the development of long term complications of diabetes.

In healthy children and adolescents, the capacity of a given blood pressure measurement to predict subsequent blood pressure has been studied using correlation coefficients between repeated measurements at different time intervals and has been shown to be rather limited.^{12,13} A similar low degree of blood pressure tracking has been reported in children with diabetes,¹⁴ suggesting that it is difficult to predict future blood pressure levels for individual patients. In agreement with these studies, we found only a small tracking correlation coefficient of blood pressure measurements repeated after four years in a cohort of 81 children with diabetes. Furthermore, of the 12 children with raised blood pressure in both sessions of measurements in study I, only five were shown to be above the defined confidence intervals for age and sex some three years later.

Microalbuminuria, that is, urinary albumin excretion which while raised is yet below the level of Albustix-positive albuminuria, has been shown in adults with diabetes to predict nephropathy.^{15,16} Microalbuminuria has been shown to be present in 12-20% of diabetic children.^{2,3} However, there is a high day to day variation in urinary albumin excretion⁸ and repeated measurements need to be performed before classifying patients as having abnormal or normal values. In study I, four 24 hour urine collections were performed, two at the start of the study and another two 6-7 months later. Only the 12 children with abnormal values in both periods were then classified as having persistent microalbuminuria. In study II, while none of these children had developed clinical proteinuria, nine (75%) still had values outside the normal range. Overall, the correlation between measurements in the two studies was small ($r = 0.28$).

The upper normal 95% tolerance limit for albumin/creatinine ratio in our study was estimated at 1.57 mg/mmol. There are very limited published data on normal values for the albumin/creatinine ratio or urinary albumin excretion in children. Davies *et al*¹⁷ defined the upper normal range for the albumin/creatinine

ratio at 1.72 mg/mmol for girls and 1.57 mg/mmol for boys, in 12 hour night urine collections from 374 normal children. Gibb *et al*¹⁸ also reported the upper normal limit of the range for the albumin/creatinine ratio to be 1.17 mg/mmol in 45 healthy children.

Limited joint mobility, a relatively common phenomenon in childhood diabetes, was detected more commonly in study II than in study I, and a high degree of coexistence with other abnormalities was noted.¹⁹

Reduced pupil size in darkness, believed to be due to autonomic neuropathy,²⁰ has been shown to be common in patients with insulin dependent diabetes mellitus.²¹ Moreover pupil size has been used in addition to cardiovascular tests as a measure of autonomic function.²² We found a close correlation ($r = 0.94$) between measurements of pupillary dilatation in darkness performed in the two studies using the same technique. Among the five children with abnormal values in study I none had developed any clinical symptoms of autonomic neuropathy, but all five had abnormal pupillary response to darkness in study II. For the group as a whole, PD% in study II was found to be significantly decreased compared with study I. This is likely to represent a diabetes effect, as the sympathetic dysfunction due to aging noted in non-diabetic populations is not demonstrable in childhood.⁶

In this cohort study we have identified a group of diabetic children and adolescents with persistent abnormalities. However, 15 children and adolescents were identified (M/F 6/9; mean age 15.7 years; disease duration 7.8 years), who despite having a mean HbA_{1c} of $> 10\%$ throughout the period between the two studies, did not have any measurable abnormalities in either study.

We conclude that early subclinical changes of renal and autonomic function in a cohort of children with diabetes reassessed after four years were (with the exception of blood pressure measurements) relatively consistent, with some pointers to a progression in the number of children showing abnormalities and the degree of abnormality. Further follow up is necessary to establish whether these findings reliably predict the long term development of clinical complications. If this proves to be the case then the tests could be used to identify patients for trials of targeted treatment to improve glycaemic control or alternative interventions such as the use of angiotensin converting enzyme inhibitors. Conversely, it remains to be shown whether persistently normal test results identify a population of patients who, despite indifferent control, appear to be at a relatively lower risk of developing the complications of diabetes: were this to be the case it might justify a different and more relaxed approach to glycaemic control in such children.

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