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Impaired intellectual development in children with Type I diabetes: association with HbA_{1c}, age at diagnosis and sex

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Abstract

Aims/hypothesis. Good metabolic control in diabetic children is already crucial before puberty to prevent diabetic complications later in life. However, tight metabolic control could increase the risk of severe hypoglycaemia, which might be responsible for impaired intellectual performance later in life. The purpose of this prospective longitudinal study was to evaluate the relevance of long-term metabolic control and hypoglycaemia possibly affecting the intellectual development of young children with Type I (insulin-dependent) diabetes mellitus.
Methods. The intellectual development in 64 diabetic children between the ages of 7 and 16 years was assessed at least four times using the German version of the Hamburg Wechsler intelligence scale for preschool children, Children-Revised and by the "Adaptives Intelligenz Diagnostikum" (Adaptive Intelligence Diagnosticum). Data were analysed longitudinally compared with a control group.
Results. A significant decline in performance by age 7 and in verbal intelligence quotient between age 7 and 16 years was observed in diabetic boys diagnosed before the age of 6 but not in those diagnosed later and not in diabetic girls. The deterioration of intellectual performance in boys diagnosed at a very young age was not associated with the occurrence of severe hypoglycaemic episodes but was correlated with the degree of metabolic deterioration at diagnosis and with high long-term average of glycated haemoglobin.
Conclusion/interpretation. Our study in diabetic children shows that the male sex, diagnosis at a young age, metabolic condition at diagnosis and long-term metabolic control, rather than experienced hypoglycaemic attacks are risk factors for intellectual development. [Diabetologia (2002) 45: 108–114]

Keywords Child, diabetes, longitudinal, intellectual development, cognitive development, sex, hypoglycaemia, glycated haemoglobin, ketoacidosis.

Treatment, and even more so, care of children with Type I (insulin-dependent) diabetes mellitus is a difficult and demanding task for parents as well as for health professionals. Aiming for good metabolic control is often hindered by the dynamics of the disease, an insufficiency of insulin therapy, the impossibility of an exact control of carbohydrate intake and the irregularities of daily life. The knowledge of the risk of long-term vascular complications and the permanent uncertainty of threatening hypoglycaemia as an immediate complication, is a great burden for the responsible paediatric diabetologist and thus narrows his or her therapeutic possibilities.

There is now clear evidence that poor long-term metabolic control is the crucial factor for developing late vascular complications [1 – 3]. In addition, there is growing evidence that the quality of metabolic control even during pre-pubertal years greatly influences

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Abbreviations: SDS, Standard deviation score; SES, socio-economic status; IQ, intelligence quotient.

the development of nephropathy and retinopathy after puberty [4, 5]. Thus, metabolic control with the long-term goal of an HbA_{1c} average of less than 7.5% [1] is imperative even during childhood. However, such tight metabolic control could increase the risk of severe hypoglycaemia [6, 7] and a history of severe hypoglycaemic attacks during childhood is believed to be responsible for lower intellectual performance in diabetic patients compared with normal same-aged adolescents [8–13].

The goal of our study was to prospectively evaluate intellectual development in diabetic children diagnosed at a young age. We investigated the impact of severe hypoglycaemic attacks and the relevance of long-term metabolic control on intellectual development. A prerequisite for such a study is the stability and constancy of the study cohort. The children attending our Diabetes Centre of the Department of Endocrinology and Diabetology at the University Children's Hospital in Zurich fulfil these criteria. In addition, experience in neurodevelopmental testing and in the evaluation of longitudinal data sets is required. This expertise is offered by our Growth and Development Centre carrying out longitudinal studies since 1954. With this background, the "Zurich Longitudinal Study on Growth and Development of Diabetic Children Diagnosed at Young Age" was established in 1985. Since then, all children younger than 10 years of age with newly diagnosed Type I diabetes who attended our outpatient Diabetes Centre have been enrolled in this study which allows us to carry out an initial evaluation of the collected data.

Subjects and methods

Design of the "Zurich Longitudinal Study on Growth and Development of Children with Type I Diabetes Diagnosed at Young Age". More than 95% of children with Type I diabetes living in the Zurich area, representing about 25% of the total of Swiss children and adolescents with diabetes, attend the Diabetes Centre of the University Children's Hospital in Zurich [14]. Since 1985 all children with Type I diabetes diagnosed before 10 years of age could be enrolled in this prospective longitudinal study; all families initially agreed to take part in this long-term project. To date, 164 children have been included, representing an accumulated experience of 953 patient-years. Seven children had to be excluded because of non-diabetes related diseases, such as epilepsy, perinatal complications or the presence of trisomy 21, factors which were likely to hamper intellectual and neuromotor development. We have had to accept 25 dropout patients, amounting to 78 patient-years (8.2%) primarily because their families left the Zurich area. All children and their parents gave their informed consent. The study has been carried out in accordance with the declaration of Helsinki as revised in 1996.

Diabetes management and control of the study population. All children were admitted to our outpatient Diabetes Clinic after initial treatment of newly diagnosed Type I diabetes under hospital conditions, either in our hospital or one of the regional paediatric clinics. Children younger than 12 years of age were treated with an insulin schedule of at least two injections, using individual mixtures of short-acting and intermediate-acting insulin. Adolescents are treated according to a schedule using multiple (4 to 5) injections of short-acting and long-acting insulin. Much effort is put into instruction for preventing severe hypoglycaemia, based on home glucose monitoring four to six times daily. Our therapeutic and instructional approach is based on insulin dose adjustment at home by the parents or the adolescent himself, with the possibility of 24-h feedback from an on-call paediatric diabetologist of our clinic. To avoid nocturnal hypoglycaemia, we recommend sporadic nightly blood glucose control. The patients are seen at least every 3 months in our outpatient Diabetes Clinic. Episodes of severe hypoglycaemia are carefully recorded, these being defined as attacks of unconsciousness with or without seizures. In the vast majority of cases, the parents or the adolescent called the clinic immediately after a hypoglycaemic episode had occurred.

Glycated haemoglobin A_{1c} is measured at each visit. Before 1994, HbA_{1c} was measured using chromatography (Bio-Rad Laboratories, Munich, Germany), and thereafter, the DCA 2000 Analyser (Bayer, Leverkusen, Germany) was applied. When the two methods were switched, one hundred HbA_{1c} tests were carried out in parallel using both methods, thus allowing the recalculation and comparison of HbA_{1c} values obtained throughout the longitudinal study. The mean HbA_{1c} in the non-diabetic and normal control subjects is 5.2 ± 0.8% (mean ± 2 SD). The long-term HbA_{1c} was calculated as the mean of the average yearly values.

Neurodevelopmental assessment. Each child is tested annually at his birthday (± 2 weeks). The compliance in the study is as high as 98.8%, as only 12 tests out of all possible have been missed by the patients since 1985. Intellectual performance is tested at the ages of 2, 3, 4, 5, 7, 9, 11, 13, 14 and 16 years, whereas neuromotor development is examined at the ages of 6, 8, 10 and 12 years; at the age of 12 and 15 a quality of life questionnaire is carried out with the patient and their parents. The standard time for intellectual testing was assigned to be the early afternoon hours. Before examination, a blood glucose test was carried out in diabetic children to exclude a low value that might have hampered the child's performance.

Characterization of the cohort evaluated: intellectual assessment. We present longitudinal data on the intellectual development in a subgroup of 64 children of the entire cohort tested at least four out of six times between the age of 7 and 16 years. Their intellectual performance was assessed by the German version of the Wechsler Preschool and Primary Scale of Intelligence (HAWIVA) at age 7 [15], the German version of the Wechsler Intelligence Scale for Children-Revised (HAWIK-R) at age 9 and 14 [16] and the "Adaptives Intelligenz Diagnostikum " (AID) at the age of 11, 13 and 16 years [17]. For one analysis all diabetic children of the entire study, who have been tested at age 7 (girls $n = 37$, boys $n = 30$) have been included. All diabetic children were examined by the same person (D. Schoenle) being trained in the Growth and Development Centre where the control children of the Zurich Longitudinal Studies were tested by experienced developmental paediatricians. Socio-economic status (SES) was estimated by means of a six-point scale for both paternal occupation and maternal education; the lowest combined SES score was 2, the highest 12 [18].

Data analysis and statistics. The data on intellectual development collected prospectively were analysed in a longitudinal

Table 1. Characterization of the subgroup of patients evaluated longitudinally between 7 and 16 years of age. Age at diagnosis of Type 1 diabetes, metabolic control and frequency of severe hypoglycaemic episodes

	Age-group (years)	Girls			Boys		
		mean ± SD	(*n*)	range	mean ± SD	(*n*)	range
Age at diagnosis (years)	< 6	4.2 ± 1.4	13	1.4–5.8	3.9 ± 1.6	14	1.1–5.7
	6–10	7.6 ± 1.1	25	6.2–9.7	7.4 ± 1.2	12	6.1–9.7
Average HbA_{1c} (%)	< 6	7.8 ± 0.5	13	7.2–8.5	7.9 ± 0.8	14	6.0–8.8
	6–10	7.8 ± 1.0	25	5.9–9.7	7.5 ± 0.6	12	6.7–8.6
Severe hypoglycaemia (per 100 patient-years)	< 6		15.6			5.9	
	6–10		12.5			3.2	

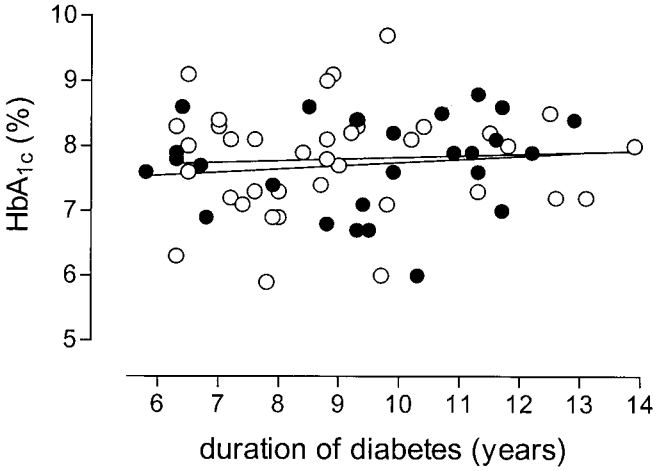


Fig. 1. Correlation between average HbA_{1c} at age 16 years and duration of diabetes in girls (●, $n = 38$) and boys (○, $n = 26$)

manner. Because different intelligence tests had to be used at the various ages IQ-SDS were calculated and used throughout; the reference group consisted of 179 (90 girls, 89 boys) healthy, non-related term subjects of the Zurich longitudinal studies carried out at the Growth and Development Centre, Children's Hospital, Zurich. To evaluate the role of the age at diagnosis the children were divided in two groups: children with preschool age of diabetes onset (< 6 years) and those with primary school onset age (6–10 years). In view of the large inter-subject variation in intellectual development, individual intelligence quotient (IQ) change from 7 to 16 years was summarized by the slope of the least square line through the observed test values. Thus, the slope is a parameter of long-term IQ development. A strong predictor for the slope was, because of the regression to the mean, the initial IQ-SDS value for verbal and performance IQ. To meaningfully compare slope values between groups the initial IQ-SDS value had to be controlled by the use of multiple regression. A p value of less than 0.05 was considered significant.

Results

The relevant demographic and metabolic parameters of the study population are shown (Table 1). Among the 64 diabetic children, the long-term HbA_{1c} was 7.8% and similarly distributed among both sexes. It did not differ between the 27 children diagnosed before age 6 and those 37 diagnosed between 6 and 10 years of age. There was no significant association between the long-term average HbA_{1c} and the duration of diabetes (Fig. 1). Long-term average HbA_{1c} also did not correlate with SES [$p = 0.56$ for girls, $p = 0.59$ for boys (data not shown)]. The frequency of episodes of severe hypoglycaemia was 10.1 per 100 patient-years in the study population; all episodes occurred after the age of 6. The frequency was significantly higher in girls than in boys ($p < 0.005$) and did not differ between those children diagnosed before age 6 and those diagnosed between 6 and 10 years of age (Table 1). The higher frequency of severe hypoglycaemic episodes in females is not completely understood but is partly explained by three girls with multiple individual episodes, which was not found in males. The SES was equal in girls (7.4 ± 2.5) and boys (7.2 ± 2.7) and comparable to that of the control children.

The results of the longitudinal evaluation of intellectual development in diabetic children based on the SDS slope of verbal and performance IQ between the age of 7 and 16 are shown (Fig. 2). To evaluate the impact of hypoglycaemic episodes, the diabetic girls and boys were divided into those who had experienced at least one episode of severe hypoglycaemia and those without hypoglycaemia. The two groups did not differ in their average HbA_{1c}: It was 7.6 ± 0.2% in 17 boys without severe hypoglycaemia, 7.9 ± 0.2% in 9 boys with hypoglycaemic episodes ($p = 0.21$), whereas it was 7.6 ± 0.2% in 19 girls without severe hypoglycaemia and 8.0 ± 0.2% in 19 girls with hypoglycaemic episodes ($p = 0.24$). Neither of the two groups (with or without hypoglycaemic episodes) differed in their verbal and performance IQ nor did they differ from the control group (Fig. 2, $p = 0.25$ to $p = 0.50$, Wilcoxon). A further division into girls or boys diagnosed before age 6 or between the age of 6 and 10 years did not show any significant differences ($p = 0.17$ an $p = 0.88$, respectively). Thus, average intellectual development was comparable to that of non-diabetic children and was not influenced by the occurrence of severe hypoglycaemia, independent of the age at diagnosis.

A significant dependence of verbal IQ in boys diagnosed before the age of 6 on average HbA_{1c} was

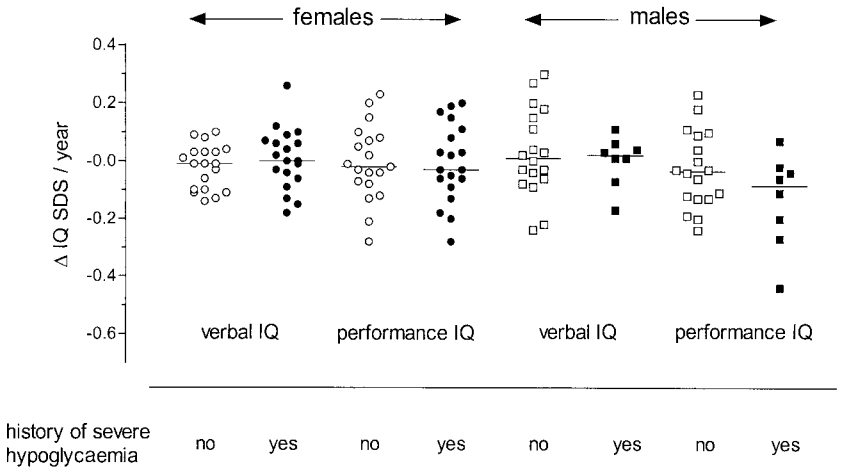
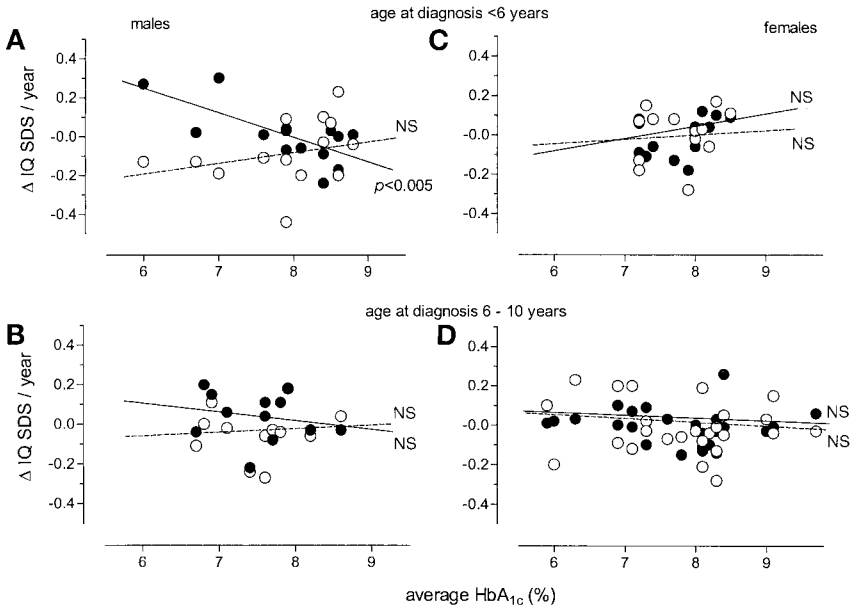


Fig. 2. Development of verbal IQ and performance IQ between 7 years and 16 years expressed as the slope (least square line through the observed test values of at least four measurements, out of six possible) in girls (● ○) and boys (□ ■) with or without a history of experienced episodes of severe hypoglycaemia

found (Fig. 3). The higher the average HbA_{1c}, the more likely was a negative slope (Fig. 3A). In the multiple regression analysis the coefficient of HbA_{1c} was negative indicating a weaker regression to the mean for those subjects with a higher HbA_{1c}; for HbA_{1c} greater than about 8% the expected value of the slope was negative suggesting a progressive loss in verbal IQ. The deterioration of the verbal IQ was not related to socioeconomic status ($p = 0.53$) and to the occurrence of severe hypoglycaemia ($p = 0.38$). This was not true for girls of both age groups (Fig. 3C, D) and for boys of the older age group (Fig. 3B). There was also no significant correlation between performance IQ and HbA_{1c}.

The results led us to analyse the possible influence of metabolic parameters and duration of disease on intellectual development in diabetic children diagnosed before age 6. All children of the ongoing longitudinal study diagnosed before the age of 6, who have been tested at age 7 (30 boys and 37 girls), were evaluated (Fig. 4). In boys we found a highly significant deficit in performance IQ at age 7 ($p < 0.001$) depending on the age at diagnosis, average HbA_{1c} between age at diagnosis and 7 years and on the severity of metabolic conditions at diagnosis using the capillary pH as a marker for degree of ketoacidosis

Fig. 3 (A–D). Development (slope) of verbal IQ (○) and performance IQ (●) between age 7 and 16 depending on the long-term average glycated haemoglobin in boys (**A**, **B**) and girls (**C**, **D**) with Type I diabetes diagnosed before age 6 (**A**, **C**) or between age 6 and 10 (**B**, **D**)



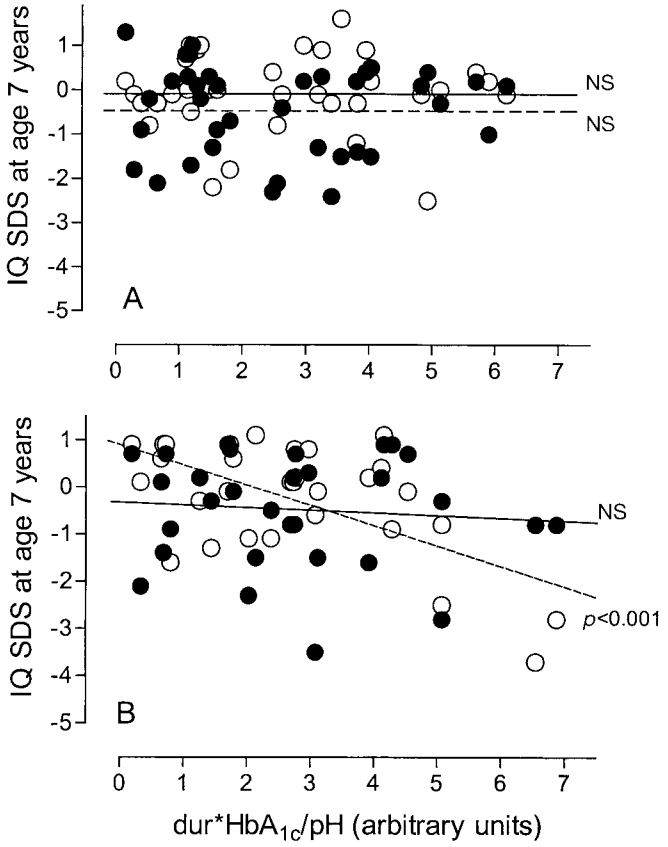


Fig. 4. Verbal IQ (○) and performance IQ (●) at age 7 in girls (**A**) and boys (**B**) with Type I diabetes diagnosed before age 6: correlation to duration of diabetes and average glycated haemoglobin at age 7 and capillary blood pH at diagnosis

(Fig. 4B). Thus, the younger the boy at diagnosis of Type I diabetes, the lower the pH at diagnosis and the higher the average HbA_{1c} by age 7, the lower was the performance IQ at age 7. No significant correlations were noted for verbal IQ in boys at age 7 ($p = 0.65$) and for verbal IQ ($p = 0.99$) as well as for performance IQ ($p = 0.93$) in girls (Fig. 4A).

Discussion

The prospective character of "The Zurich Longitudinal Study on Growth and Development of Children with Type I Diabetes Diagnosed at Young Age" and a high compliance of patients and parents allowed a detailed analysis of the individual intellectual development between 7 and 16 years of age and its correlations with hypoglycaemic events and metabolic parameters.

A most intriguing observation was that episodes of severe hypoglycaemia did not have a statistically significant impact on the development of the intellectual performance, either in girls or boys. This finding contradicts the traditional belief that diabetic children suffering from hypoglycaemic episodes during preschool age perform intellectually less than their non-diabetic peers at the end of puberty. However, the literature on this issue is controversial. Most studies showing an association between experienced hypoglycaemia and intellectual outcome [8–13] were of a cross-sectional and retrospective nature, while to our knowledge, only two studies were designed in a prospective and longitudinal manner [19, 20]. These studies followed patients of different ages from the onset of Type I diabetes for 7 [19] or only 2 [20] years longitudinally. Our study is long-term, covering the entire period from diagnosis of diabetes in early childhood to the post-pubertal age, when maturation of cerebral function is believed to be completed. In addition, our children are tested at the same ages and their development is analysed according to duration of the disease, age at diagnosis, hypoglycaemic events and metabolic parameters.

A causal association between multiple episodes of hypoglycaemia and intellectual outcome was not found. However, the possible influence of severe hypoglycaemia occurring before age 6 for later intellectual performance could not be evaluated in this study. No episode of severe hypoglycaemia was recorded between diagnosis and age 6 years in the 27 children diagnosed before 6 of age, accounting for 23.5 patient-years in girls and 29.9 patient-years in boys. To date, 89 children diagnosed before 6 years of age, including several children who experienced severe hypoglycaemic episodes during the first years of diabetes, have been enrolled in our study. The longitudinal study design will enable us to analyse their outcome when they have reached at least age 14 years.

We do not want to downplay the possible negative consequences of frequent episodes of severe hypoglycaemia on brain development during childhood. It is our therapeutic strategy in young diabetic children to achieve acceptable metabolic control and to prevent severe episodes of hypoglycaemia. The metabolic control obtained in all our children taking part in the longitudinal study proves that good control of diabetes can be achieved without taking on a high risk for severe hypoglycaemia. It has been shown in a large multicentre survey, where our diabetes centre was taking part, that good metabolic control in young children does not necessarily coincide with a high frequency of severe hypoglycaemic events [21, 22].

The lack of episodes of severe hypoglycaemia at an age younger than 6 years provided an opportunity to study the impact of age at diagnosis and metabolic factors in more detail. The evaluation confirms previous reports that intellectual deficits are more pronounced in children who developed diabetes at preschool age [8, 10]. However our results support young age as a risk factor only in males and indicate a major role of long-term metabolic control. These findings suggest that already in this age group, high average blood glucose concentrations might be a risk factor

for normal brain development. Similar observations have been made in studies of adults with diabetes showing deficits in cognitive function in patients having poor metabolic control [23–25].

In contrast to verbal IQ, the performance IQ seems not to be affected by long-term metabolic control. This, however, held no longer true when we analysed metabolic parameters before the age of 7. There was a deterioration of performance IQ strongly dependent not only on the long-term metabolic control and age at diagnosis but also on the severity of ketoacidosis (expressed by capillary pH) at diagnosis. This correlation was highly significant for performance IQ in boys only. Thus, the younger the age at diagnosis, the more severe the degree of ketoacidosis and the higher the average HbA_{1c} the greater the deterioration of performance IQ at age 7 years in boys. At preschool age, performance IQ seems to be a more sensitive indicator for intellectual deterioration than verbal IQ and a less sensitive indicator at school age.

Thus we hypothesized that in children of preschool age the acute metabolic condition at the beginning of the disease together with long-term metabolic control of Type I diabetes influences intellectual development with a decline of performance IQ at a very young age and no further deterioration thereafter, whereas a decline of verbal IQ development commences at school age. Only boys with Type I diabetes diagnosed before age 6 are at risk, not older boys and not females at any age of diagnosis. Our study shows an intriguing difference between the sexes in the intellectual development of young diagnosed diabetic children. The cause of this sex difference is not known but correlates with data [26] showing learning difficulties more in diabetic boys than in girls. There is also evidence of increased vulnerability of brain development in young boys [27, 28].

Taking into account that this first evaluation of our study is based on a limited number of 64 children, we concluded that males but not females, with Type I diabetes diagnosed at a young age show a decline of intellectual performance in comparison with non-diabetic control subjects. Brain development in diabetic boys diagnosed at a young age seemed to be less affected by episodes of severe hypoglycaemia rather than by the severity of metabolic condition at presentation of the disease and by a long-term high average of blood glucose.

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