Predictors of Change in the Neuropsychological Profiles of Children With Type 1 Diabetes 2 Years After Disease Onset

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OBJECTIVE — To identify type 1 diabetes–related predictors of change in the neuropsychological profiles of children over the first 2 years of the illness.

RESEARCH DESIGN AND METHODS — Children (n = 116) aged 3–14 years were assessed soon after diagnosis and re-evaluated 2 years later to examine relationships between illness variables, such as age of onset and metabolic control history, and changes in neuropsychological status over the first 2 years of type 1 diabetes.

RESULTS — Illness variables were significant predictors of change in neuropsychological test scores within 2 years of onset of type 1 diabetes. Age of onset of type 1 diabetes predicted negative change on Performance Intelligence Quotient, whereas both recurrent severe hypoglycemia and chronic hyperglycemia were associated with reduced memory and learning capacity.

CONCLUSIONS — These results suggest that the relationship between metabolic control and neuropsychological risk is nonlinear in that children with either recurrent severe hypoglycemia or chronically elevated blood sugars exhibit negative changes in their neuropsychological profiles. Onset of type 1 diabetes very early in life adds another dimension of risk, particularly affecting the acquisition of visuospatial skills.

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Selective neuropsychological deficits have been demonstrated in both adult and pediatric patients with type 1 diabetes and are likely to be associated with parameters of metabolic control (1,2). There is evidence that both serious hypoglycemia and chronic hyperglycemia alter central nervous system (CNS) function and may increase the likelihood of neuropsychological impairment (3). Other proposed risk factors for neuropsychological sequelae include early age of disease onset, long duration of type 1 diabetes, and the presence of biomedical complications such as neuropathy, retinopathy, nephropathy, and vascular disease (1).

A constant supply of glucose is essential for normal cerebral metabolism because the capacity of the brain to store and synthesize carbohydrate is limited (4). During hypoglycemia, cerebral glucose and oxygen availability are reduced, producing a partial energy failure of the CNS. Hypoglycemia-related CNS energy failure is associated with excessive release of the excitatory neurotransmitters, glutamate and N-methyl-D-aspartate (NMDA), which literally stimulate affected neurons to death (3). Previous research has demonstrated that neuronal necrosis after severe hypoglycemia is most likely to occur in the middle layers of the cerebral cortex and hippocampus, possibly because of the relatively high proportion of NMDA receptors in this region (5,6).

There are a number of reports linking a history of recurrent severe hypoglycemia with neuropsychological deficit (7–11), although significant associations are not always established (12,13). Two large-scale longitudinal studies (14,15) found no evidence for hypoglycemia-related neuropsychological impairment, but did not include young children in their samples. McCall and Figlewicz (3) point out that glucose transport and utilization may differ in children, who are likely to be particularly sensitive to glucose deprivation because of heightened energy requirements related to brain growth and development. The difficulties inherent in obtaining accurate retrospective reports of hypoglycemia may also contribute to inconsistent findings.

Chronically elevated blood glucose levels affect cerebral glucose metabolism and impair cerebral blood flow, leading over time to cerebrovascular disease and structural CNS changes (3). Hence, one would expect to find relationships between chronic poor control and neuropsychological deficit in type 1 diabetic populations. Cognitive deficits in adults with a history of chronic hyperglycemia are most evident in those with type 1 diabetic complications such as neuropathy or retinopathy (12). Since these complications are not seen in children before adolescence, it was thought that hyperglycemia-related deficits would not be apparent in pediatric populations, and this belief was

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Abbreviations: CNS, central nervous system; COWAT, Controlled Oral Word Association Test; DKA, diabetic ketoacidosis; IQ, intelligence quotient; NMDA, N-methyl-D-aspartate; RAVLT, Rey Auditory Verbal Learning Test; RCH, Royal Children's Hospital, Melbourne; T1, assessment at clinic visit 3 months after diagnosis (baseline); T2, assessment between 2 years and 2 years, 4 months after baseline; WISC-R, Wechsler Intelligence Scale for Children, Revised; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence, Revised.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

supported by null findings in several pediatric studies (12,16). However, these studies used a single concurrent measure of glycosylated hemoglobin as their index of hyperglycemia. This measure provides no information about metabolic control history beyond the previous 2–3 months; hence, relationships between significant periods of poor metabolic control in the past and current neuropsychological status were not actually tested.

An association between early onset (before 5 years of age) and poorer cognitive abilities was first reported by Ack et al. (17) and has since emerged as one of the strongest risk factors for neuropsychological sequelae in children with type 1 diabetes (12,16,18). Ryan (2) has suggested that the "early onset" effect is a surrogate for the impact of hypoglycemia on an immature brain. He points out that very young children are more likely to experience serious hypoglycemia because they lack the capacity to perceive and communicate early symptoms, their food intake and activity levels are unpredictable, and they may have a heightened sensitivity to insulin. They are also more likely to be adversely affected by hypoglycemia because of the greater vulnerability of the developing brain to a metabolic insult. Rovet et al. (19) agree that there may be a critical period of increased cerebral sensitivity to the effects of type 1 diabetes, but have suggested an alternative (and not mutually exclusive) hypothesis: that chronic hyperglycemia may disrupt myelin formation in very young children still experiencing brain development. They point out that animal studies have shown that type 1 diabetes affects myelination because of defective incorporation of acetate and glucose into nerve lipids (20). The alternative hypotheses of Ryan (2) and Rovet et al. (16) suggest a nonlinear relationship between neuropsychological dysfunction and glycemic control, i.e., patients with low blood sugar levels (good metabolic control) but frequent hypoglycemia and those with chronically high blood sugar levels may both be at risk for neuropsychological sequelae, although for different reasons. Furthermore, the nature and extent of neuropsychological impairment may vary as a function of the neurodevelopmental status of the child at disease onset.

The present study is a prospective examination of the effects of type 1 diabetes on neuropsychological functioning in a large and representative cohort of children. This report focuses on the relationship between metabolic variables and change in cognitive performance over time. Sample characteristics and neuropsychological profiles of the type 1 diabetic and control subjects at diagnosis and 2 years later have been described in previous reports (21,22). Duration of type 1 diabetes and treatment procedures were controlled, since clinical care was provided at a single tertiary center with all children enrolled at diagnosis and followed up at specified intervals. Relevant data about disease variables were recorded prospectively. Neuropsychological test selection focused on measures of attention, speed of processing, memory, new learning, and executive functions because it has been shown that the frontal and temporal regions of the brain are particularly affected by abnormal blood glucose levels (1,5,6). Furthermore, measures of attention, processing speed, and memory are particularly sensitive to subtle decrements in cognitive function (23) and to deterioration occurring over a relatively brief period of time (24). The neuropsychological profile of children with type 1 diabetes did not differ from that of a community control group when assessed soon after diagnosis (21). Two years later, children with type 1 diabetes tended to show more negative change, relative to control subjects, in their standardized scores on measures of general intelligence, significantly so on the vocabulary and block design subtests (22). Multivariate group differences were also apparent on composite variables measuring speed of processing and learning. The present report describes relationships between parameters of the illness and neuropsychological change within the type 1 diabetic cohort 2 years after diagnosis. It was hypothesized that negative changes in neuropsychological functioning would be associated with parameters of the illness such as disease onset before 5 years of age, a history of recurrent severe hypoglycemia and/or hypoglycemic convulsions, and chronic hyperglycemia.

RESEARCH DESIGN AND METHODS

— Children (3–14 years of age) who presented to The Royal Children's Hospital, Melbourne (RCH) with newly diagnosed type 1 diabetes from September 1990 to December 1992 formed the study population. This is a representative sample, in that virtually all children with type 1 diabetes living within the metropolitan region and close environs of Melbourne are initially treated at RCH. Children were not enrolled in the study if they did not anticipate any further attendance at RCH (n = 18), had a premorbid history of CNS disease or trauma (n = 4), or if neither parent spoke sufficient English to give informed consent and complete questionnaires (n = 3). Of the 134 eligible children, 123 subjects were enrolled, a participation rate of 92%. Socioeconomic status of the cohort did not differ from that of a community control group (type 1 diabetes 4.5 ± 1.2, control 4.5 ± 1.3, $P > 0.05$).

A baseline neuropsychological assessment was conducted at the child's clinic visit 3 months after diagnosis (T1). Blood glucose levels were determined before assessment by finger-prick testing using a Reflolux-S Home Blood Glucose Monitor (Boehringer Mannheim, Melbourne, Australia). If a child had a blood glucose reading <4 mmol/l, they were given a fast-acting carbohydrate snack, and testing proceeded after a short interval. All children were assessed on an age-appropriate measure of general intellectual ability. Tests of specific neuropsychological functions were added to the protocol for children aged ≥7 years. Tests were administered in a standard order. Subjects were reassessed between 2 years and 2 years, 4 months after the baseline assessment (T2). The project was approved by Royal Children's Hospital Ethics in Human Research Committee.

Measures

The Wechsler Preschool and Primary Scale of Intelligence, Revised (WPPSI-R) (25) and the Wechsler Intelligence Scale for Children, Revised (WISC-R) (26) were used to assess general intelligence in children aged 3–6 and ≥7 years, respectively. The WPPSI-R contains virtually the same subtests and measures abilities similar to those measured by the WISC-R and has been specifically revised to facilitate comparison of a child's abilities over time. The validity, test-retest stability, and reliability of both instruments are well established.

Neuropsychological tests

Digit Span. This subtest of the WISC-R (26) measures attention and short-term memory for auditory/verbal information. The child is asked to repeat in sequence, and then in reverse order, random strings of numbers of increasing length. Digit Span scores are not used to calculate verbal or full scale intelligence quotient (IQ).

Rey Auditory Verbal Learning Test. This test assesses the ability to acquire new verbal information (27). A 15-item word list is presented over five trials to establish a learning curve, and a sixth delayed recall trial (Rey Auditory Verbal Learning Test [RAVLT] 6) is

administered after an interference task to assess the degree to which new learning has been consolidated in long-term memory. The efficiency of retrieval of learned information (RAVLT retrieval) is measured by calculating the difference between the child's score on RAVLT 6 (spontaneous recall) and his or her ability to identify the target words when embedded within a short prose passage (cued recall).

Lhermitte Board. This test is a measure of spatial memory and visual learning in which the child is asked to recall the spatial location of nine pictures of common objects presented over multiple trials (27). Scores were calculated for *1*) the number of spatial positions recalled after the first trial as a measure of immediate visual memory span (Lhermitte Board 1) and 2) the number of trials required to reach criterion (three consecutive correct trials) as a measure of visual learning (Lhermitte Board criterion).

Controlled Oral Word Association Test. The Controlled Oral Word Association Test (COWAT) is a measure of verbal fluency and conceptual reasoning (27). The child is asked to generate words beginning with each of the letters F, A, and S as quickly as possible, allowing 60 s per letter. Subjects were instructed that proper names and repetitions or different forms of the same word (e.g., run, runs, running) are not acceptable. The score for this measure was the total number of acceptable words across all three letter categories.

Rey Complex Figure Test. The Rey Complex Figure Test is a design copying test that measures planning and organization of complex visuoperceptual information, graphomotor skills, and visual memory (27). The child is asked to copy a complex geometric figure using four pencils of different colors. By recording the order in which the colors are used, the examiner can establish the organizational strategies used by the child. After the administration of another task, and without forewarning, the child is asked to redraw the figure from memory. Separate scores were calculated for accuracy of copy, organizational strategy, and recall of the design (percent of copy recalled after a brief delay).

The selected neuropsychological tests are widely used in research and clinical practice and are well accepted as valid measures of the variables of interest (23,27).

Metabolic control history

As part of standard medical care at RCH, parents and/or older children were asked to measure and record blood glucose levels at least three times each day. Compliance with this request was very high, but it is acknowledged that there may be some under-reporting of unrecognized episodes, particularly nocturnal events. The close relationship established between investigators and study participants minimized the risk of fictitious reports. Parents were also asked to note episodes of diabetic ketoacidosis (DKA) and of altered conscious state, convulsions, or coma associated with hypoglycemia as they occurred, thus avoiding the problems of retrospective recall. Corroboration of this information was obtained from the hospital record. Glycosylated hemoglobin levels (HbA_{1c}) were measured at clinic visits every 3 months using the Bayer DCA 2000 (Bayer, Elkhart, IN) method (normal reference range 4.5−5.7%). An overall measure of hyperglycemia was determined by calculating the percentage of time from diagnosis when HbA_{1c} was >9.5%.

Statistical analyses

Standard multiple or simultaneous regression was the statistical technique chosen for data analysis. This is an early report of findings in a longitudinal study, and further follow-up of this cohort is planned. It was important to make no a priori assumptions about the relative strength of predictor variables. In the standard model, all predictor variables are entered into the regression equation simultaneously (28). Each variable is then evaluated in terms of what it adds to the predictive model that is distinct from the predictability provided by all other independent variables.

Partial correlation coefficients are reported as a measure of the strength of the relationship between the dependent variable and each single predictor variable when the effects of all other predictor variables are held constant. A partial *t* value is also reported to indicate the additional contribution of each variable above all others in the equation. Systat for Windows, Version 5, was used to perform all statistical analyses, and the significance level was set at $P = 0.05$. However, significant trends are also noted, since any changes in the neuropsychological status of type 1 diabetic children apparent so early in the course of the illness are likely to be subtle. Identification of early trends will guide subsequent follow-up of this cohort.

RESULTS

— Seven children assessed at T1 did not participate in the second stage of the study. This article reports findings based on the data from 116 children (94% of the original sample) who were assessed at both T1 and T2. There were 55 boys and 61 girls in the sample, and mean age at study entry was 7.5 ± 3.7 years (range 3–14). Children who did not continue in the study after the baseline assessment (T1) did not differ on IQ, demographic, or metabolic control variables from those who were assessed at both stages. Group mean blood glucose level at the commencement of testing was 14 ± 5.9 mmol/l. Pearson product moment correlations were used to examine relationships between concurrent blood glucose level and test scores. A positive correlation between T2 test blood glucose level and Performance IQ ($r = 0.26$, $P = 0.05$) was the only significant finding. Group mean scores on metabolic control variables are presented in Table 1.

Analysis of variance was used to examine age of onset effects on biomedical variables. There was a significant age of onset effect on the number of serious hypoglycemic episodes, defined as a recorded blood sugar level <2 mmol ($F = 11.16$, df = 1,117, $P = 0.001$), with early-onset children recording more episodes. It was not possible to examine statistically age of onset effects on frequency of convulsions because only one child with onset before 5 years had experienced such an event.

Standard multiple regression analyses were used to examine relationships between metabolic control variables and T1-T2 change on measures of general intelligence. After controlling for the T1 score on the relevant variable, the following predictor (independent) variables were entered in the equation:

- Age at disease onset, entered as a dichotomous categorical variable, i.e., onset before or after 5 years.
- Total number of blood sugar levels <2 mmol/l per child as a measure of frequency of severe hypoglycemia. The criterion <2 mmol/l was set because empirical findings are mixed on the impact of milder levels of hypoglycemia on cognitive function, but there is consensus that neuroglycopenic symptoms are an invariable correlate of blood sugar levels below 2 mmol/l. It was also felt that blood sugar levels as low as this were more likely to be noticed and recorded reliably than less severe incidents. To normalize the distribution of this skewed variable, scores were categorized into four levels, <5, 5–14, 15–39, and ≥40 episodes.

Table 1—*Type 1 diabetes variables 2 years after disease onset*

Medical variable	*n*	All	*n*	Early onset (<5 years)	*n*	Later onset (>5 years)	*P*
Mean HbA_{1c}	115	7.4 ± 1.2	18	7.4 ± 1.0	97	7.4 ± 1.2	NS
Mean % HbA_{1c} >9.5	115	23.2 ± 26.4	18	20.2 ± 24.8	97	23.7 ± 26.8	NS
Mean total blood sugar level <2 mmol/l	110	15.3 ± 10.5	18	22.9 ± 22.3	92	13.8 ± 20.0	0.001
Test blood sugar level (mmol/l)	111	14.0 ± 5.9	17	11.2 ± 5.0	94	14.6 ± 6.0	NS
Convulsions (number of children)	116	16	18	1	98	15	

Data are means ± SD, unless otherwise indicated.

- Convulsions, treated as a dichotomous categorical variable (i.e., positive or negative history) to control for the highly skewed distribution. Episodes of altered conscious state were not included in these analyses because it was felt that it would be impossible to establish cross-informant reliability.
- Percentage of time spent in poor control, calculated by dividing the number of HbA_{1c} measurements >9.5% by the total number of available measurements over the study period, multiplied by 100.

Because all children assessed on these measures at both time points were aged >5 years at diagnosis, age at disease onset was deleted from the above set of predictor variables in the regression analyses of neuropsychological functions. However, T2 test age was included as a predictor variable because age-standardized scores were not available for these measures. Episodes of DKA were not used in the analyses because of the very small number of children (n = 7) who had experienced an episode from diagnosis to T2. Since highly collinear variables can distort the results of multiple regression analyses, correlations between biomedical variables were examined; none met the criterion for multicollinearity.

The general intelligence of children aged from 3 to <5 years at onset of type 1 diabetes (n = 18) was assessed at both time points using the WPPSI-R. Children aged 6 years at diagnosis were assessed with the WPPSI-R (n = 19), and those aged ≥7 years with the WISC-R (n = 79), at T1. All later-onset children were re-evaluated at T2 using the WISC-R. Because the focus of interest was on change in relative performance on the neuropsychological test measures, these analyses were limited to those children (n = 69) who were old enough to have been evaluated on these specialized tests at both assessments (i.e., age of type 1 diabetes onset ≥7 years). Significant findings are presented in Table 2.

Type 1 diabetes onset before 5 years was associated with negative T1-T2 change on Performance IQ. Recurrent severe hypoglycemia predicted negative T1-T2 change on a test of attention and short-term memory (Digit Span), and both recurrent severe hypoglycemia and chronic hyperglycemia were associated with poorer performance on measures of learning/consolidation (Lhermitte Board criterion, RAVLT 6) and less efficient spontaneous retrieval from long-term memory (RAVLT retrieval). Chronic hyperglycemia also predicted a lower organization score on the Rey Figure. There were no diabetes-related predictors of T1-T2 change in Verbal IQ score, Lhermitte Board total score, COWAT total word score, or the Rey Figure copy and recall scores.

CONCLUSIONS — A number of significant relationships between biomedical indices and neuropsychological change were found within 2 years of type 1 diabetes onset. The current findings are largely consistent with hypothesized relationships between illness variables and neuropsychological outcomes and with previous empirical reports. Onset of type 1 diabetes before 5 years of age predicted negative change on Performance IQ, as had been reported in our previous examination of control versus type 1 diabetic group differences 2 years after disease onset (22). Future administration of the more specialized neuropsychological measures to children with early onset of disease will be necessary to establish whether this age-group is vulnerable to adverse illness effects over a wider range of cognitive processes. It is clear though, that difficulties are not confined to this age-group. In the older children who were administered the specialized neuropsychological tests, both chronically elevated blood glucose levels and recurrent severe hypoglycemia were associated with subtle performance decrements within 2 years of type 1 diabetes onset.

The association between early onset of type 1 diabetes and a decline in Performance IQ scores is consistent with earlier findings (12,16), suggesting that type 1 diabetes, or some aspect of the illness, has an impact on the development of visual processing skills in the very young child. Ryan (2) has argued that the "early onset" effect is a surrogate for the impact of recurrent episodes of hypoglycemia on the developing brain. He suggests that the effect will be most evident on measures of "fluid intelligence" assessed on the Performance Scale of the Wechsler tests (e.g., rapid visual scanning, visuospatial problem–solving, visuographic, and motor planning skills). Rovet et al. (16,19) agree that early-onset children are an "at risk" subgroup, but have suggested an alternative hypothesis: that chronic hyperglycemia disrupts myelin formation in very young children. Children with poorly myelinated nerve fibers will process information more slowly (29) and are likely to perform less efficiently on timed tasks such as those that make up the Performance Scale.

In this study, there was no statistical relationship between the measure of chronic hyperglycemia and negative change on the Performance Scale, while children with onset before 5 years of age were both more likely to have recurrent episodes of severe hypoglycemia (although not convulsions, possibly because of heightened parental surveillance) and to show a decline in Performance IQ. Thus, the results of the current study provide more immediate support for Ryan's suggestion that it is recurrent hypoglycemia that is detrimental to a developing brain (2). However, deficits associated with subtle early cerebral compromise may be silent initially, only becoming apparent when skills fail to emerge at the developmentally appropriate time. Longer-term follow-up of the early-onset children using a more extensive range of neuropsychological measures will be necessary before the full impact of type 1 diabetes on the young brain becomes clear.

Recurrent hypoglycemia was associated with negative T1-T2 change on a measure of attention and immediate memory. Associations between severe hypoglycemia and attentional and memory deficits

Table 2—*Significant biomedical predictors of T1-T2 change on measures of general intelligence and neuropsychological functions*

Dependent variable	Mental process	*n*	R^2	Significant predictors	Partial correlation coefficient	Partial *t* value	*P*
Performance IQ	Nonverbal intelligence	106	0.219	Onset age	0.233	2.527	0.01
Digit Span	Short-term memory	71	0.170	Hypoglycemia <2 mmol/l	−0.327	−2.653	0.01
Lhermitte Board 1	Short-term memory	69	0.704	HbA_{1c}% >9.5	−0.161	−2.154	0.04
Lhermitte Board criterion	Learning	69	0.653	Hypoglycemia <2 mmol/l	0.348	2.065	0.04
				HbA_{1c}% >9.5	0.191	1.779	0.08*
RAVLT 6	Learning	68	0.627	HbA_{1c}% >9.5	−0.231	−2.775	0.01
				Hypoglycemia <2 mmol/l	−0.179	−2.055	0.04
RAVLT retrieval	Learning	68	0.609	HbA_{1c}% >9.5	0.172	2.016	0.05
				Hypoglycemia <2 mmol/l	0.171	1.907	0.06*
Rey Organization	Organization	68	0.492	HbA_{1c}% >9.5	−0.205	−2.092	0.04

Lhermitte Board criterion and RAVLT retrieval are negatively scored. *Trend significance levels.

have been reported previously in pediatric studies (8,10), although findings from adult studies have been less conclusive (1,13–15). The selective vulnerability of the hippocampal region to excitotoxic cell damage during severe hypoglycemia has been well demonstrated (5,6), and the immature brain may be especially susceptible to insult. These structures play an important role in the efficient encoding of novel information (30). In the current study, severe recurrent hypoglycemia was also associated with less efficient learning and consolidation into long-term memory, possibly because of disruption to the initial stages of encoding in short-term memory. Poorer spontaneous retrieval of information from long-term memory is consistent with previous empirical evidence that children with a history of severe hypoglycemia exhibit less efficient information processing strategies (8,11). The small number of children who had experienced a hypoglycemic convulsion during the first 2 years of type 1 diabetes (n = 16) may account for the failure to establish a statistical link between convulsive episodes and adverse neuropsychological sequelae in the present study. However, the current findings do suggest that recurrent hypoglycemic events short of convulsions may be associated with subtle reductions in mental efficiency in pediatric populations.

Chronic hyperglycemia appeared to compromise organizational strategy use and new learning/consolidation across both visual and verbal modalities. Memory deficits have been consistently associated with poorly controlled type 2 diabetes (31), but studies of type 1 diabetic adults have produced inconsistent findings (1,13). There is a single report of memory dysfunction in children with poorly controlled type 1 diabetes (32), but these investigators relied on a parental rating of "general metabolic control," and it is not clear whether parents included a history of hypoglycemic events as well as chronic hyperglycemia in their estimate. In addition, the participation rate in this study was quite low, and the sample may not have been a representative one. Methodological deficiencies may explain the null findings in other pediatric studies, since investigators have relied either on a single measurement of glycosylated hemoglobin (12,16) or a mean of all available readings (33). A mean may wash out the effect of extreme scores.

The mechanisms by which hyperglycemia might compromise learning and organizational strategies in children are not clear. Psychogenic explanations are sometimes invoked to explain performance decrements in type 1 diabetic patients (2). As previously reported (22), there were no significant correlations between Child Behavior Checklist summary scores and neuropsychological test performance; hence, there is no evidence that emotional factors are influencing the current findings. Chronically elevated blood glucose levels have been linked to decreased cerebral blood flow and reduced glucose metabolism in adult patients with long duration of both type 1 (3) and type 2 (31) diabetes. However, while atherosclerotic changes might explain deficits in long-duration adult patients, they are a less plausible explanation in children with relatively recent onset type 1 diabetes. Animal models suggest that myelin production is impeded in the presence of high blood glucose (20). The negative impact of poorly myelinated nerve fibers on information-processing capacities may be a more convincing explanation for deficient strategy use and memory deficits in prepubertal children with type 1 diabetes (29). The findings of the current study support a hypoglycemia-related effect on attention and immediate memory, mediated by selective damage to the hippocampus, while chronic hyperglycemia impacts later stages of the information processing chain, reducing learning capacity and impeding consolidation of information into long-term memory. These interpretations will remain speculative until studies combining neuroimaging and neuropsychological measures are conducted.

As early as 2 years after disease onset, it was possible to discern significant relationships between type 1 diabetes variables and performance decrements. It should be stressed that the proportion of total variance in T1-T2 change scores explained by biomedical predictors was small. As noted in a previous report of this cohort (22), the test scores of children with type 1 diabetes remain within average limits, and deficits of the magnitude reported are unlikely to be of functional significance at this point. However, it is of concern that it was possible to discern significant effects of type 1 diabetes on test performance at all so early in the course of the illness, when the number of children who had experienced severe metabolic crises was still low. The nature of the cognitive process that appear vulnerable to disease-related impairment is also of concern. If children attend to, and acquire, new knowledge even marginally less efficiently than their peers, they will be placed at a cumulative disadvantage for classroom learning.

A number of limitations in the current study are acknowledged. The investigators were not blinded to the group membership (type 1 diabetic vs. control), since blood glucose levels were measured in the clinical group and the children were asked to report symptoms of hypoglycemia during testing should these occur. However, there was minimal room for subjectivity in the scoring of the selected tests and the likely direction of bias, should it exist, would be to minimize group differences. The assessment of children across developmental stages necessitated the use of different tests at different ages. Specific neuropsychological processes could not be evaluated at all in the younger children, the subgroup possibly at greatest risk. Even with a prospective design, reliable ascertainment of the incidence of hypoglycemia may be undermined by both innocent and deliberate underreporting. Glycoslylated hemoglobin, while the best available, is still an imperfect measure of longer-term metabolic control.

A large and representative cohort of children with newly diagnosed type 1 diabetes has been assembled and comprehensively assessed soon after disease onset and 2 years later. The prospective and controlled design permits relationships between disease variables and neuropsychological performance to be determined and provides an opportunity to study the evolution of type 1 diabetes–related neuropsychological change within a developmental framework. If the current findings are replicated and extended in future follow-up of this cohort, and in other prospective studies of similar design, they will highlight the dilemma for those involved in the clinical care of children with type 1 diabetes. Intensified treatment regimes have demonstrated that it is possible to achieve significant reductions in glycosylated hemoglobin levels, but at increased risk of severe hypoglycemia (14,15). Longer-term follow-up of this cohort will further enhance knowledge about the neuropsychological sequelae of type 1 diabetes and the implications for optimal clinical management.

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