Neuropsychological Profiles of Children With Type 1 Diabetes 6 Years After Disease Onset

ELISABETH A. NORTHAM, PHD[1,2]
PETER J. ANDERSON, BA, GRAD DIP (APP PSYCH)[1,2]
RANI JACOBS, BSC, GRAD DIP[1,2]
MATTHEW HUGHES, BBUS, GRAD DIP[1,2]
GARRY L WARNE, MBBS, MD[3]
GEORGE A. WERTHER, MBBS, MD[3]

OBJECTIVE — To describe neuropsychological profiles and their relationship to metabolic control in children with type 1 diabetes 6 years after the onset of disease.

RESEARCH DESIGN AND METHODS — Children with type 1 diabetes ($n = 90$), aged 6–17 years, who had previously been assessed soon after diagnosis and 2 years later, were reevaluated 6 years after the onset of disease. Their neuropsychological profiles were compared with those of individuals in a community control group ($n = 84$), who had been assessed at similar intervals. Relationships between illness variables, such as age at the onset of disease and metabolic control history, and neuropsychological status were also examined.

RESULTS — Six years after onset of disease, children with type 1 diabetes performed more poorly than control subjects on measures of intelligence, attention, processing speed, long-term memory, and executive skills. Attention, processing speed, and executive skills were particularly affected in children with onset of disease before 4 years of age, whereas severe hypoglycemia was associated with lower verbal and full-scale intelligence quotient scores.

CONCLUSIONS — Neuropsychological profiles of children with type 1 diabetes 6 years after the onset of disease are consistent with subtle compromise of anterior and medial temporal brain regions. Severe hypoglycemia, particularly in very young children, is the most plausible explanation for neuropsychological deficits, but the contributory role of chronic hyperglycemia warrants further exploration.

Diabetes Care 24:1541–1546, 2001

A constant supply of glucose is critical for normal cerebral metabolism. Therefore, it is not surprising that functional and structural changes within the central nervous system have been documented in patients with type 1 diabetes (1,2). In adults, neuropsychological deficits are most evident in those with the biomedical complications associated with chronic hyperglycemia (3). Findings from large-scale prospective studies (4) suggest that adults are resilient to hypoglycemia-related effects on neuropsychological functions, although this point is still debated. In children, early age at onset of illness and a history of severe hypoglycemia have emerged as the most consistent risk factors for neuropsychological sequelae in children (2,5–9). However, the specific cognitive skills affected have varied across studies, and the timing, severity, and frequency of hypoglycemic insult required to inflict permanent cerebral dysfunction have yet to be defined.

Ryan and Becker (2) have suggested that the "early onset" effect is a surrogate for the impact of hypoglycemia on an immature brain. They point out that very young children are more likely to experience serious hypoglycemia because they lack the ability to perceive and communicate early symptoms and their food intake and activity levels are unpredictable. In addition, young children may be more sensitive than adults to glucose deprivation because of heightened energy requirements related to brain growth and development. Rovet et al. (6,8) agree that there may be a critical period of increased cerebral sensitivity to the effects of type 1 diabetes but have suggested an alternative, but not mutually exclusive, hypothesis that chronic hyperglycemia may disrupt myelin formation and neurotransmitter regulation in the developing brain.

Small and unrepresentative samples, retrospective collection of metabolic control history, and cross-sectional designs that provide no information about cognitive status before exposure to adverse metabolic events limit the conclusions that can be drawn from previous studies. Rovet and Ehrlich (7) followed children during a 7-year period from diagnosis, but the sample size was small ($n = 16$). An increased incidence of hypoglycemic seizures in very young children has made it difficult to establish whether early onset and hypoglycemia act synergistically or independently to compromise neuropsychological functions. The possible impact of chronic hyperglycemia on prepubertal children has never been tested adequately, because most studies have used a single concurrent measure of HbA_{1c} as the index of hyperglycemia. This provides no information about metabolic control history beyond the previous 2–3 months.

This study reports findings of a 6-year follow-up of a large and representative cohort of children with type 1 diabetes who were assessed serially on neuropsycho-

From the [1]Department of Psychology, Royal Children's Hospital, Melbourne; the [2]Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne; and the [3]Department of Endocrinology/Diabetes, Royal Children's Hospital, Melbourne, Australia.

Address correspondence and reprint requests to Elisabeth Northam, Department of Psychology, Royal Children's Hospital, Parkville, Victoria, 3052, Australia. E-mail: northaml@cryptic.rch.unimelb.edu.au.

Received for publication 27 October 2000 and accepted in revised form 16 May 2001.

Abbreviations: CFT, Complex Figure Test; COWAT, Controlled Oral Word Association Test; IQ, intelligence quotient; RAVLT, Rey Auditory Verbal Learning Test; SES, socioeconomic status; WISC-III, Wechsler Intelligence Scale for Children—3rd edition.

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

logical measures since onset of illness. Sample characteristics and neuropsychological profiles of the clinical and control subjects at diagnosis and 2 years later have been described in previous reports (10–12). Duration of illness and treatment procedures were controlled because clinical care was provided at a single tertiary center, with all children enrolled at diagnosis and followed at specified intervals. Metabolic control variables were recorded prospectively. Neuropsychological test selection focused on measures of attention, processing speed, memory, new learning, and executive functions, because it has been shown that the prefrontal cortex and medial temporal regions of the brain are particularly affected by abnormal blood glucose levels (1,2). Furthermore, measures of attention, processing speed, and memory are sensitive to subtle decrements in cognitive function (13). The neuropsychological profile of children with type 1 diabetes did not differ from that of a community control group when assessed soon after diagnosis (10). Two years later, children with type 1 diabetes tended to show more negative change in measures of general intelligence and performed more poorly on processing speed and learning (11). Early age of onset predicted negative change on measures of intelligence quotient (IQ), whereas both recurrent severe hypoglycemia and chronic hyperglycemia were associated with reduced memory and learning capacity (12). This report describes neuropsychological profiles after 6 years of exposure to the metabolic perturbations associated with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Sample

The cohort has been fully described in previous reports (10–12). This is a representative sample, because virtually all children within the metropolitan region and close environs of Melbourne, Australia, were treated initially at the Royal Children's Hospital, Melbourne. Exclusion criteria were premorbid history of central nervous system disease, trauma, or non–English-speaking parents. Children attending Royal Children's Hospital 6 years after onset of disease (i.e., those younger than 12 years of age at diagnosis) formed the study population for the third phase of the study. Of the eligible subjects, 80 children aged 3–11 years at onset of disease and 74 control subjects who had been assessed previously 3 months after diagnosis (T1) and 2 years later (T2) agreed to participate in the third phase (T3). Three eligible subjects and four control subjects declined to participate. An additional seven control subjects could not be traced; therefore, the participation rate was 96% for the clinical cohort and 87% for the control subjects. Ten children with diabetes diagnosed before 3 years of age were also been evaluated serially at T1 and T2, and all agreed to participate in the T3 assessment. Control subjects for this subset of children were obtained for the third stage of the project by contacting the schools that had provided the original control sample. Children ($n = 10$) of the same sex whose birthday most closely matched that of a child with diabetes were invited to participate in the third phase of the study. Socioeconomic status (SES) of the two groups was similar (children with type 1 diabetes: $n = 10$, [means ± SD] 3.4 ± 0.5 SES score; control subjects: $n = 10$, 3.4 ± 1.3; NS). Thus, the final sample for T3 comprised children with type 1 diabetes ($n = 90$) and control subjects ($n = 84$).

Procedure

The T3 assessment included a standardized test of general intelligence and tests of specific neuropsychological functions. All subjects completed the same battery (described in MEASURES), and tests were administered in a standardized order. Blood glucose levels of the children with type 1 diabetes were measured before testing. If a child had a blood glucose level <4 mmol/l, they were given a fast-acting carbohydrate snack, and testing proceeded after a brief interval. The project was approved by Royal Children's Hospital Ethics in Human Research Committee.

Measures

Socioeconomic status was measured using the Daniel Scale of Occupational Prestige (14). This scale is based on occupation and provides a six-point rating scale (1 = high to 6 = low SES).

The Wechsler Intelligence Scale for Children –Third Edition (WISC-III) (15) was used to assess general intelligence.

Neuropsychological tests

Attention. Digit Forwards, a test of the ability to attend to and register sequentially presented auditory/verbal information, is adapted from the Digit Span subtest of the WISC-III (15). Code Transmission (16) measures sustained attention for auditory information. The child is asked to identify a target stimulus presented at 2-s intervals via audiotape over 12 min. Scores are obtained for targets identified correctly, omitted targets, and nontarget responses. Sky Search (16) assesses the child's ability to identify a visual target against background distraction. The Digit Forwards raw score, targets correctly identified and targets omitted on Code Transmission, and targets correctly identified on Sky Search were used to measure focused and sustained attention for verbal information, attentional lapses, and selective attention for visual information, respectively.

Processing speed. Symbol Search, a subtest of the WISC-III (15), requires rapid visual scanning, perceptual analysis, and motor response. Sky Motor (16) assesses simple motor speed. The Contingency Naming Test (17) is a cross-modal task requiring speeded visual input/verbal output under conditions of increasing complexity. It measures mental flexibility and self-monitoring skills as well as processing speed. Symbol Search scale score, Sky Motor time score, and the time taken to complete four trials of the Contingency Naming Test were used to assess processing speed.

Immediate memory. Story Memory and Design Memory (18) measure immediate recall of prose and visuo-graphic information, respectively. The Rey Auditory Verbal Learning Test (RAVLT) (19) assesses the ability to acquire new verbal information. A 15-item word list is presented over five trials to establish a learning curve. The child is later asked, without forewarning, to recall the list (spontaneous recall) and to identify words from the list embedded within a short prose passage (cued recall). Visual Learning (18) assesses the ability to acquire new visual information presented over four trials. Graphic designs are presented in a particular location on a board, and the child is asked to remember which spatial location is associated with each design. Raw scores for the initial trials of the RAVLT and Visual Learning as well as Design Memory and Story Memory total raw scores were

Table 1—*Significant group differences on measures of general intelligence 6 years after onset of diabetes*

	Type 1 diabetes		Control subjects		Significance	
Measure	*n*	Score	*n*	Score	Group	Group × age at onset
Verbal IQ						
All	90	97.4 (1.5)	84	103.2 (1.5)	$P < 0.01$	NS
Onset <4 years	24	98.4 (2.5)	27	106.6 (2.4)	$P < 0.01$	NS
Onset >4 years	66	96.2 (1.5)	57	99.7 (1.7)	$P < 0.01$	NS
Performance IQ						
All	89	103.6 (1.8)	83	106.8 (1.8)	NS	NS
Onset <4 years	24	103.2 (3.1)	27	107.2 (2.9)	NS	NS
Onset >4 years	65	104.1 (1.9)	56	106.4 (2.0)	NS	NS
Full-scale IQ						
All	89	100.2 (1.6)	83	105.3 (1.5)	$P < 0.05$	NS
Onset <4 years	24	100.5 (2.7)	27	107.3 (2.6)	$P < 0.05$	NS
Onset >4 years	65	99.9 (1.6)	56	103.2 (1.8)	$P < 0.05$	NS

Data are adjusted least-square means (SE).

used to assess immediate recall in both the verbal and visual modalities.

New learning. The total scores, summed over five trials of the RAVLT and over four trials of Visual Learning were used to assess acquisition of new information with repeated exposure.

Long-term memory. The delayed recall trials (spontaneous and cued) of the RAVLT, the Complex Figure Test recall score (19) (described in EXECUTIVE FUNCTIONS), and the Visual Learning and Story Memory delayed recall scores were used to assess long-term memory.

Executive functions. The Controlled Oral Word Association Test (COWAT) (19) is a measure of verbal fluency/concept formation and the ability to shift set and inhibit incorrect responses. The Complex Figure Test (CFT) (19) is a design-copying task that measures planning and organization of complex visuoperceptual information and graphomotor skills. After a time delay, the child is asked, without forewarning, to copy the design again from memory. The Tower of London (19) is a measure of planning and problem-solving ability, in which the child is required to reproduce models of increasing complexity, presented on stimulus cards, in a specified number of moves. Making Inferences (20) assesses the child's ability to infer meaning from ambiguous or incomplete complex linguistic information. The total word score on the COWAT, the copy score of the CFT, problems correctly solved on the Tower of London, and the Making Inferences total score were used to assess executive functions.

Self-monitoring. Errors (i.e., repetitions and incorrect responses) on the COWAT, self-corrections and errors on the Contingency Naming Test, and intrusions (nonlist words) on the RAVLT were used to assess self-monitoring.

Metabolic control history

Parents were asked to report episodes of severe hypoglycemia associated with convulsion or coma occurring at any time since diagnosis. HbA_{1c} was measured at each 3-month clinic visit using the Bayer DCA 2000 method (normal reference range 4.5−5.7%).

Statistical analyses

Systat for Windows software (version 5; Systat, Evanston, IL) (21) was used to perform statistical analyses.

RESULTS — There were no significant group differences in age (children with type 1 diabetes: 12.1 ± 2.9; control subjects: 12.1 ± 2.8; NS), sex distribution (children with type 1 diabetes: 45 girls, 45 boys; control subjects: 44 girls, 40 boys; NS), or SES (children with type 1 diabetes: 3.8 ± 1.2; control subjects: 4.0 ± 1.5; NS) at T3. Examination of the baseline data of T3 participants revealed no significant group difference on full-scale IQ at T1 (children with type 1 diabetes: 107.7 ± 16.5; control subjects: 109.6 ± 13.4; NS).

General intelligence

Analysis of variance was used to examine group differences and effects of age of onset on verbal, performance, and full-scale IQ (Table 1). Preliminary analyses showed that effects related to age of onset were most apparent if the group was dichotomized into children with onset of disease before 4 years of age and those with onset of disease at 4 years or older. In each analysis of variance, the dependent variable was the IQ score, and the independent variables were group (type 1 diabetes, control), and age of onset (early onset younger than 4 years, later onset 4 years and older). SES was entered as a covariate. There were significant main effects on verbal ($F = 8.07$, $P < 0.01$) and full-scale IQ ($F = 5.33$, $P < 0.05$); children with type 1 diabetes obtained lower scores. Group differences on Performance IQ were not significant. Examination of group by interaction of age of onset with measures of general intelligence revealed no significant findings.

Neuropsychological functions

Multivariate analysis of covariance was used to determine group main effects and group by age of onset interactions on the neuropsychological composites: attention, processing speed, immediate memory, new learning, long-term memory, executive functions, and self-monitoring (Table 2). Test age and SES were entered as covariates.

There was a significant group main effect ($F = 2.63$, $P < 0.05$) and group age at onset interaction ($F = 2.85$, $P < 0.05$) on attention. Results of post hoc tests showed that children with type 1 diabetes, particularly those with onset of disease before 4 years of age, identified fewer

Table 2—*Significant group differences on neuropsychological clusters 6 years after onset of diabetes*

Measure	Type 1 diabetes			Control subjects			Group	Group onset age
	All	<4 years	>4 years	All	<4 years	>4 years	(*P*)	(*P*)
n	90	24	66	84	27	57		
Attention							<0.05	<0.05
Code correct	35.3 (0.6)	34.1 (1.3)	36.5 (0.6)	37.3 (0.6)	37.1 (0.6)	37.5 (0.7)	0.01	NS
Code omissions	2.4 (0.5)	2.6 (1.0)	2.2 (0.5)	1.4 (0.5)	1.5 (0.9)	1.2 (0.6)	NS	NS
Digits forward	8.2 (0.3)	8.9 (0.5)	7.5 (0.3)	8.5 (0.2)	8.9 (0.5)	8.1 (0.3)	NS	NS
Sky targets	18.5 (0.3)	18.6 (0.5)	18.4 (0.3)	18.3 (0.2)	18.6 (0.5)	18.0 (0.3)	NS	NS
Processing speed							<0.01	NS
CNT total time	193.6 (5.9)	221.6 (12.1)	165.6 (6.1)	166.5 (5.6)	180.4 (11.3)	152.7 (6.8)	<0.01	0.06
Sky time	100.8 (4.1)	114.0 (8.9)	87.5 (4.6)	95.9 (4.1)	100.1 (8.4)	91.6 (5.1)	NS	NS
Symbol search	10.4 (0.4)	10.2 (0.9)	10.7 (0.5)	11.9 (0.4)	12.7 (0.8)	11.1 (0.5)	0.01	0.06
Immediate memory							NS	NS
RAVLT1	5.4 (0.2)	5.0 (0.4)	5.9 (0.2)	5.9 (0.2)	5.8 (0.4)	6.0 (0.3)	0.06	NS
Story recall	25.7 (1.2)	22.4 (2.4)	29.0 (1.2)	26.5 (1.1)	25.0 (2.2)	28.0 (1.3)	NS	NS
Visual learning 1	5.8 (0.3)	6.0 (0.6)	5.5 (0.3)	5.3 (0.3)	5.5 (0.6)	5.0 (0.3)	NS	NS
Design memory	30.9 (1.1)	30.1 (2.2)	31.6 (1.2)	31.2 (2.2)	31.0 (2.0)	31.3 (1.2)	NS	NS
New learning							NS	NS
RAVLT—5 trials	49.1 (1.1)	47.3 (2.1)	50.9 (1.1)	50.6 (1.0)	48.6 (2.0)	52.5 (1.2)	NS	NS
Visual learning	29.9 (1.2)	31.1 (2.5)	28.9 (1.3)	28.1 (1.2)	28.9 (2.3)	27.4 (1.4)	NS	NS
Long-term memory							<0.01	NS
RAVLT—spontaneous	11.4 (0.4)	11.7 (0.7)	11.1 (0.4)	11.4 (0.3)	11.6 (0.7)	11.2 (0.4)	NS	NS
RAVLT—cued	13.0 (0.2)	12.3 (0.4)	13.7 (0.2)	13.6 (0.2)	13.2 (0.4)	13.9 (0.2)	<0.05	NS
Visual learning	8.9 (0.4)	9.3 (0.8)	8.6 (0.4)	8.3 (0.4)	8.1 (0.8)	8.5 (0.5)	NS	NS
Rey figure recall	17.4 (0.8)	16.8 (1.7)	18.0 (0.9)	20.1 (0.8)	21.0 (1.6)	19.2 (0.9)	0.01	NS
Story recall	23.3 (1.3)	19.2 (2.6)	27.4 (1.3)	23.9 (1.2)	21.9 (2.4)	25.8 (1.4)	NS	NS
Executive skills							<0.01	<0.05
Rey figure copy	27.6 (0.7)	26.8 (1.3)	28.4 (0.7)	30.7 (0.7)	31.7 (1.4)	29.7 (0.8)	<0.01	0.05
COWAT total words	25.9 (1.0)	26.8 (2.1)	24.9 (1.0)	26.5 (1.8)	26.2 (2.1)	26.8 (1.2)	NS	NS
Making inferences	8.7 (0.2)	8.0 (0.5)	9.5 (0.2)	9.4 (0.2)	9.3 (0.5)	9.5 (0.3)	<0.05	<0.05
TOL completed trials	11.3 (0.1)	11.4 (0.2)	11.3 (0.1)	11.7 (0.1)	11.8 (0.2)	11.7 (0.1)	<0.01	NS
Self-monitoring							<0.01	NS
COWAT errors	1.6 (0.2)	1.5 (0.4)	1.8 (0.2)	1.1 (0.2)	0.6 (0.4)	1.6 (0.3)	<0.05	NS
Code no-targets	2.4 (0.6)	3.4 (1.2)	1.4 (0.7)	0.4 (0.6)	0.1 (1.2)	0.8 (0.7)	<0.01	0.08
CNT12 err&sc	1.3 (0.2)	1.2 (0.4)	1.4 (0.2)	1.4 (0.2)	1.4 (0.3)	1.3 (0.2)	NS	NS
CNT34 err&sc	11.8 (1.1)	14.7 (2.3)	8.9 (1.2)	7.6 (1.1)	8.0 (2.1)	7.1 (1.3)	<0.01	NS
RAVLT intrusions	1.5 (0.2)	2.1 (0.4)	0.9 (0.2)	1.0 (0.2)	1.4 (0.4)	0.5 (0.3)	0.08	NS

Data are least-square adjusted means (SE). CNT, Contingency Naming Test. TOL, Tower of London.

correct targets on Code Transmission. There was a significant group main effect ($F = 4.81$, $P < 0.01$) and a group age at onset trend ($P < 0.06$) on processing speed. Results of post hoc tests showed significantly slower times for children with early onset type 1 diabetes. There were no significant main or interaction effects on immediate memory or new learning. A significant group effect ($F = 3.58$, $P < 0.01$) was found on long-term memory, but the group age at onset interaction was not significant. Significant main ($F = 4.57$, $P < 0.01$) and group age at onset interaction effects ($F = 2.60$, $P < 0.05$) were found on executive functions. Results of post hoc tests showed that children with early onset type 1 diabetes performed more poorly than children with later-onset type 1 diabetes or control subjects. There was a significant group main effect ($F = 4.00$, $P < 0.01$) but no group age at onset interaction on self-monitoring.

Repeated-measures analyses revealed no significant group differences on neuropsychological measures common to both T1 and T3 assessments (CFT, RAVLT, and COWAT) using data from the subset of children who had been old enough to complete them at study entry (i.e., those aged 7 years and older at T1: children with type 1 diabetes, $n = 40$; control subjects, $n = 38$).

Relationship between metabolic control variables and neuropsychological status

Mean concurrent HbA_{1c} for the children with type 1 diabetes was 8.5 ± 1.2% (clinic average 8.8 ± 1.5%). Mean blood glucose level before testing was 14.5 ± 6.2 mmol/l. A total of 25 children had experienced at least one seizure associated with hypoglycemia. The percentage of children with a positive seizure history was similar across the early onset (25%) and later-onset (27%) groups. A measure

of chronic hyperglycemia was formed by calculating the percentage of time from diagnosis that the child had recorded poor control (defined as HbA_{1c} >9.5%). Stepwise multiple regression analyses were conducted to examine the relationship between metabolic control variables and neuropsychological functioning on measures for which significant group (type 1 diabetes, control) differences had been found. For age-standardized measures, SES was entered first, with seizure history (yes or no), and percentage of total HbA_{1c} measurements >9.5% entered on the second step. Age at time of testing was also entered on the first step for unstandardized measures. SES and seizure history were significant predictors of verbal IQ ($r^2 = 0.201$, $P < 0.01$) and full-scale IQ ($r^2 = 0.126$, $P < 0.05$); seizure history accounted for 6 and 3% of the variance, respectively. Children with a positive seizure history obtained lower scores. The regression analyses for IQ measures were repeated, entering the T1 score as an additional predictor variable, with similar findings. There was a trend ($P < 0.1$) for seizures to be associated with reduced self-monitoring (more errors on COWAT and trials 3 and 4 of the Contingency Naming Test).

CONCLUSIONS — Six years after onset of disease, children with type 1 diabetes performed more poorly than control subjects on measures of intelligence, attention, processing speed, long-term memory, executive functions, and self-monitoring. Clinical and control groups had not differed on a measure of full-scale IQ at T1. Attention, processing speed, and executive functions were particularly affected by onset of illness before 4 years of age, whereas history of seizures was associated with lower scores on measures of verbal and full-scale IQ and a tendency to make more errors on complex tasks. There were no significant relationships between chronically elevated blood glucose levels and neuropsychological deficit test scores, using the definition of hyperglycemia devised for this study.

In the current study, verbal IQ seemed to be more sensitive to illness effects than performance IQ, consistent with previous reports of subtle language deficits in children with type 1 diabetes, which become more apparent as duration of illness increased (6,9,22–24). The current findings are also consistent with those of Rovet and Ehrlich (7), who found that 7 years after onset of disease, verbal IQ had declined significantly, particularly in those children with early onset of disease and/or history of seizures. The explanation for the verbal deficits noted in children with type 1 diabetes remains speculative. Reduced stores of overlearned verbal knowledge may reflect a semantic memory deficit, secondary to hypoglycemia-related hippocampal damage in a developing brain. Alternatively, vigilance and sustained attention are particularly sensitive to transiently lowered blood glucose levels (2), and these skills are critical for effective classroom learning. Children prone to recurrent hypoglycemia may learn less optimally over time, leading to cumulative deficits in verbal knowledge, even when cerebral structures are not permanently damaged.

Deficits in attention (6,7,22), executive skills (22), and processing speed (5,8) have been reported in previous studies of children with type 1 diabetes, consistent with the current findings. Deficits in attention and processing speed may be linked to the longer evoked potential latencies in children with type 1 diabetes (25). Hershey et al. (5) and Rovet and Ehrlich (7) identified long-term visual memory impairments in children with a history of seizures, whereas in the current study, the deficit was generalized rather than confined to the subgroup with a known history of significant hypoglycemia. Performance on immediate rote memory tasks was unaffected across all studies. Hagen et al. (22) suggest that deficits in higher-level organization and strategy, aspects of executive function, explain poorer performance on complex memory and learning tasks in children with type 1 diabetes. If this is true, one would expect deficits to be less evident on rote recall tasks and more apparent on long-term recall tasks, in which success depends on well-organized encoding and storage of information.

In the current study, hypoglycemia exerted specific effects on verbal and full-scale IQ. There was also a tendency for children with history of seizures to make more errors on timed, complex tasks under conditions of stimulus overload, for example, when required to make rapid decisions about competing response choices. The association between history of seizures and language deficits has been found before (6,7,22) and forms an intriguing contrast to studies in adult patients (26), which report greater sensitivity of performance IQ to hypoglycemia. Considering findings from both pediatric and adult studies, it seems that seizures may disrupt the development of language skills but not their maintenance. This interpretation is consistent with the developmental literature, which suggests that well-consolidated skills are more resilient to the effects of subtle brain insults than skills that are evolving or are yet to emerge (13).

In the current study, attention, processing speed, and executive skills were particularly affected in children diagnosed before 4 years of age. Relationships between early disease onset and deficits in processing speed (9,22,27), memory (9,22,24), and executive skills (5,22) have been found before. Attention seems to be particularly vulnerable to early onset of disease; deficits have been reported in a number of studies (6,7,9,22,24,27), and it is possible that attentional deficits contribute to poor performance on memory, processing speed, and executive tasks.

Traditionally, the effect of early onset of diabetes has been attributed to the impact of severe hypoglycemia on a developing brain. In many previous studies (8,22,24), children with early onset of disease had experienced more seizures than children with later onset, although information about the age at which seizures actually occurred has not been provided. This makes it difficult to distinguish effects of early onset of disease from effects related to hypoglycemic seizures. In their recent report, Rovet and Alvarez (6) note that although seizures were more common in the early onset subgroup, most children experienced their first seizure after 6 years of age. In the current study, only one of the children with early onset of disease had experienced a seizure before 4 years of age, and the proportion of children with history of seizures in early and later-onset groups was similar. However, in both studies, children with early onset of disease exhibited specific deficits. These findings suggest that early onset is a risk factor for neuropsychological sequelae independent of hypoglycemic seizures, although it is still possible that deficits reflect the impact of severe hypoglycemia short of seizures. This interpretation is consistent with recent reports (28) showing high rates of nocturnal hypo-

glycemia in children with diabetes, with small children at greatest risk.

It is important to note a number of limitations of the current study. Developmental factors limit the overall prospective design of the study. Longitudinal data were available only for IQ measures and a subset of the neuropsychological measures in children aged ≥7 years at diagnosis. Despite careful definition and prospective recording of metabolic control variables, true ascertainment of hyperglycemia and hypoglycemia remains problematic. The strengths of the current investigation lie in the controlled design, the large and representative sample, and the high participation rate during the 6 years of the study. Children with type 1 diabetes and control subjects were matched on IQ at study entry. Six years later, children with type 1 diabetes exhibited subtle deficits in intelligence and specific neuropsychological functions, which were most evident in those with early onset of disease or history of hypoglycemic seizures. Early onset was established as a risk factor for neuropsychological sequelae independent of hypoglycemic seizures.

The impact of repeated episodes of severe, often unrecognized, hypoglycemia in the very young child (even when seizures are not occurring) is the most plausible explanation for neuropsychological dysfunction in children with type 1 diabetes. However, the alternative possibility, that chronically elevated blood glucose levels may impede myelination and alter neurotransmitter regulation, a process that could also have maximum impact on the small child during a stage of active brain development, warrants further exploration. These alternative hypotheses are not mutually exclusive and are of more than theoretical interest in the dilemma they pose for those engaged in the clinical management of small children with diabetes. Future studies should use new techniques in neuroimaging and in the continuous monitoring of blood glucose levels to delineate further etiological factors in neuropsychological dysfunction in children with type 1 diabetes.

Acknowledgments— This study was supported by the National Health and Medical Research Council, Australia.

We thank the children and families who so willingly gave their time to participate in this research.

References

1. McCall A, Figlewicz D: How does diabetes mellitus produce brain dysfunction? *Diabetes Spectrum* 10:25–31, 1997
2. Ryan C, Becker D: Hypoglycemia in children with type 1 diabetes mellitus: risk factors, cognitive function, and management. *Endocrinol Metab Clin North Am* 28: 883–900, 1999
3. Ryan C, Williams T, Finegold D, Orchard T: Cognitive dysfunction in adults with type 1 (insulin-dependent) diabetes mellitus of long duration: effects of recurrent hypoglycemia and other chronic complications. *Diabetologia* 36:329–334, 1993
4. The Diabetes Control and Complications Trial Research Group: Effects of intensive diabetes therapy on neuropsychological function in adults in the diabetes control and complications trial. *Ann Intern Med* 124:379–388, 1996
5. Hershey T, Craft S, Bhargava N, White N: Memory and insulin dependent diabetes mellitus (IDDM): effects of childhood onset and severe hypoglycemia. *J Int Neuropsychol Soc* 3:509–520, 1997
6. Rovet J, Alvarez M: Attentional functioning in children and adolescents with type 1 diabetes. *Diabetes Care* 20:803–810, 1997
7. Rovet J, Ehrlich R: The effect of hypoglycemia seizures on cognitive function in children with diabetes: a 7-year prospective study. *J Pediatr* 134:503–506, 1999
8. Rovet J, Ehrlich R, Hoppe M: Intellectual deficits associated with early onset of insulin-dependent diabetes mellitus in children. *Diabetes Care* 10:510–515, 1987
9. Ryan C, Vega A, Drash A: Cognitive deficits in adolescents who developed diabetes early in life. *Pediatrics* 75:921–927, 1985
10. Northam E, Anderson P, Werther G, Adler R, Andrewes D: Neuropsychological complications of insulin dependent diabetes in children. *Child Neuropsychol* 1:884–890, 1995
11. Northam E, Anderson P, Werther G, Warne G, Adler R, Andrewes D: Neuropsychological complications of insulin dependent diabetes in children two years after disease onset. *Diabetes Care* 21:379–384, 1998
12. Northam E, Anderson P, Werther G, Warne G, Andrewes D: Predictors of change in the neuropsychological profiles of children with type 1 diabetes 2 years after disease onset. *Diabetes Care* 22: 1438–1444, 1999
13. Anderson V, Northam E, Wrennall J, Hendy J: *Developmental Neuropsychology: A Clinical Approach.* Hove, East Sussex, U.K., Psychology Press, 2001
14. Daniel A: *Power, Privilege and Prestige: Occupations in Australia.* Melbourne, Longman-Cheshire, 1983
15. Wechsler D: *Manual for the Wechsler Intelligence Scale for Children*. 3rd ed. New York, The Psychological Corporation, 1991
16. Manly T, Robertson I, Anderson V, Nimmo-Smith I: *The Test of Everyday Attention for Children.* Cambridge, U.K., Thames Valley Test Company, 1999
17. Taylor H: Learning disabilities. In *Behavioral Assessments of Childhood Disorders.* Mash E, Ed. New York, Guilford Press, 1988, p. 402–405
18. Sheslow D, Adams W: *Wide Range Assessment of Memory and Learning Administration Manual.* Wilmington, DE, Jastak Associates, 1990
19. Anderson V, Lajoie G, Bell R: *Neuropsychological Assessment of the School Aged Child*. Melbourne, Melbourne University Press, 1995
20. Wing E: *The Test of Language Competence – Expanded Edition*. Sydney, The Psychological Corporation, 1989
21. Wilkinson L, Hill M, Welna J, Birkenbeuel G: *Systat for Windows. Version* 5: Evanston, IL, Systat, 1992
22. Hagen J, Barclay C, Anderson B, Feeman D, Segal S, Bacon G, Goldstein G: Intellective functioning and strategy use in children with insulin-dependent diabetes mellitus. *Child Dev* 61:1714–1727, 1990
23. Kovacs M, Goldston D, Iyengar S: Intellectual development and academic performance of children with insulin-dependent diabetes: a longitudinal study. *Dev Psychol* 28:676–684, 1992
24. Wolters C, Yu S, Hagen J, Kail R: Short-term memory and strategy use in children with insulin-dependent diabetes mellitus. *J Consult Clin Psychol* 64:1397–1405, 1996
25. Seidl R, Birnbacher R, Hauser E, Bernert G, Freilinger M, Schober E: Brainstem auditory evoked potentials and visual evoked potentials in young patients with IDDM. *Diabetes Care* 19:1220–1224, 1996
26. Deary I, Langan S, Graham K, Hepburn D, Frier B: Recurrent severe hypoglycemia, intelligence and speed of information processing. *Intelligence* 16:337–359, 1992
27. Bjorgaas M, Gimse R, Vik T, Sand T: Cognitive function in type 1 diabetic children with and without episodes of severe hypoglycaemia. *Acta Paediatr* 86:148–153, 1997
28. Davis E, Jones T: Hypoglycemia in children with diabetes: incidence, counterregulation and cognitive dysfunction. *J Pediatr Endocrinol Metab* 11:177–182, 1998