Conventional Versus Intensive Diabetes Therapy in Children With Type 1 Diabetes

Effects on memory and motor speed

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OBJECTIVE — Severe hypoglycemia may impair medial temporal–mediated cognitive skills, such as the ability to recall past events explicitly (delayed declarative memory). The objective of this study was to determine whether delayed declarative memory deficits are present in a group of diabetic children with an increased risk of severe hypoglycemia.

RESEARCH DESIGN AND METHODS — Nondiabetic children (n = 16) and children with type 1 diabetes who had been randomly assigned to either intensive (IT) (n = 13) or conventional (CT) (n = 12) diabetes therapy at the time of diagnosis participated in the study. All episodes of severe hypoglycemia were prospectively ascertained. All children were tested on memory tasks that have been closely linked to medial temporal functioning and on reaction time measures.

RESULTS — Our results demonstrated that the IT group had a threefold higher rate of severe hypoglycemia, performed less accurately on a spatial declarative memory task, and performed more slowly, but not less accurately, on a pattern recognition task than did the CT group or control subjects. In addition, both groups of type 1 diabetic children were significantly impaired on a motor speed task compared with their nondiabetic peers.

CONCLUSIONS — These results indicate a selective relative memory impairment associated with IT that is consistent with the effects of severe hypoglycemia and medial temporal damage or dysfunction. If larger prospective studies determine that severe hypoglycemia is the mediating factor for this memory impairment, extreme caution in imposing overly strict standards for glucose control in young patients with type 1 diabetes would be indicated because of the increased risk of hypoglycemia associated with IT regimens.

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Although it is generally agreed that type 1 diabetes can have a significant effect on neuropsychological function, it is unclear which clinical variables associated with type 1 diabetes pose the greatest risk for cognitive impairment and which cognitive skills are most vulnerable to these risks. The two variables that have been most commonly investigated and reliably associated with cognitive impairment are age of onset of type 1 diabetes and a history of severe hypoglycemia (1–6).

Based on neuropathological evidence (7–9), it has been proposed that severe hypoglycemia may preferentially harm neurons in the medial temporal region, specifically the hippocampus. Subsequently, severe hypoglycemia may impair medial temporal–mediated cognitive skills such as the ability to explicitly recall past events or consciously learned information after a delay (delayed declarative memory) (10,11). Case studies have reported deficits in delayed declarative memory after severe hypoglycemia (10,12) with subsequent damage to the medial temporal region (12). Previous research has also suggested that, in patients with childhood-onset type 1 diabetes, severe hypoglycemia can have a significant consequence for memory functioning that is independent of generalized disease effects (4). In one study, patients with type 1 diabetes who had a history of severe hypoglycemia demonstrated significantly impaired delayed declarative memory yet were relatively unimpaired on nondeclarative memory tasks (4). Thus, severe hypoglycemia had a specific (rather than diffuse) effect on neuropsychological functioning.

The possibility that severe hypoglycemia may be a risk factor for specific types of memory impairment in children has not been adequately tested. Other studies have measured the change in cognitive function over time in children with type 1 diabetes, but none have used particularly sensitive memory tasks (13–15). In this study, we tested whether delayed declarative memory impairment is detectable in a group of children at higher risk for severe hypoglycemic episodes. We assessed memory skills in children with type 1 diabetes who had been randomly assigned at the time of diagnosis to either intensive (IT) or conventional (CT) diabetes therapy regimens. We prospectively assessed severe hypoglycemic episodes and used experimentally derived tasks that have been closely linked to medial temporal functioning in addition to well-validated and clinically used tasks. The primary experimental tasks in this study are delayed response tasks (16–22). After damage to or disruption of components of the medial temporal region, adult

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Abbreviations: ANOVA, analysis of variance; CT, conventional therapy; DCCT, Diabetes Control and Complications Trial; DMSL, Delayed Match to Sample List Presentation; IT, intensive therapy; SDR, Spatial Delayed Response; WISC-III, Wechsler Intelligence Scale for Children, third revised edition.

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

humans and animals are able to perform accurately in trials with short delays yet are impaired in trials with longer (>15–30 s) delays (19,21,23,24). Thus, we predicted that children in the IT group would experience a higher rate of severe hypoglycemia and more impairment in delayed declarative memory (particularly as measured by delayed response tasks) compared with CT patients and control subjects.

RESEARCH DESIGN AND METHODS

Participants

A total of 16 nondiabetic children and 25 children with type 1 diabetes were tested (aged 9–18 years; Table 1). The diabetic patients were recruited from a larger study conducted at the Washington University School of Medicine and St. Louis Children's Hospital, in which 34 children (aged 6.9–16.7 years [mean 11.7]) were randomized at the time of diagnosis to either IT or CT. Children in the IT group (n = 17) were expected to measure blood glucose at least 4 times daily and use 3–4 insulin injections per day or an insulin pump to keep their preprandial blood glucose level between 70 and 120 mg/dl. Children in the CT group (n = 17) were expected to use 2–4 blood glucose determinations and 1–2 insulin injections per day to keep their preprandial blood glucose level between 80 and 180 mg/dl. The importance of avoiding severe hypoglycemia was emphasized in both groups.

Because the diabetic subjects in this study were recruited at the time of diagnosis and were carefully and prospectively followed by the study staff (M.S., N.H.W.) at least until the performance of the testing protocol, complete ascertainment of severe hypoglycemic episodes was accomplished. Severe hypoglycemia was defined by using the Diabetes Control and Complications Trial (DCCT) definition (25), that is, episodes associated with severe neurological dysfunction (e.g., seizure, loss of consciousness, disorientation, inability to arouse from sleep) that require intervention with glucagon or intravenous dextrose or milder forms of hypoglycemia associated with neurological dysfunction that were not recognized by the patient or were not self-treated. In the overall study population (n = 34), the IT group (n = 17) had 3.3 times more episodes of severe hypoglycemia than children in the CT group (n = 17) (80.0 vs. 24.4 episodes per 100 patient-years, respectively). The frequency of milder episodes of hypoglycemia, which were defined as any experience of hypoglycemic symptoms that was recognized and treated by the child or another individual before neurological impairment, was based on child or parent estimations of mild episodes during the previous month at their trimonthly visits. These data are considered to be only estimates of the true rate of mild hypoglycemia and are less reliable than the measurements of the frequency of severe hypoglycemia. Of the 34 subjects in the overall study, one was not studied because of a hearing impairment, 4 moved away from the area before the testing protocol, and 4 could not be scheduled in a timely manner. The subjects studied in the protocol included 13 from the IT group and 12 from the CT group.

In this study, 6 of the 13 IT patients experienced severe hypoglycemia, whereas only 1 of 12 CT patients did. The IT group averaged 85 episodes of severe hypoglycemia per 100 patient-years compared with 28 in the CT group. This represented a threefold higher incidence in the IT group versus the CT group. On average, the last severe hypoglycemic episode occurred 6.1 months before testing (SD = 3.3, range 3–11 months). Due to the small group of patients that had severe hypoglycemia, we had limited power to detect differences between groups with and without hypoglycemic episodes. However, we did examine the means for each group and perform an exploratory repeated-measures analysis of variance (ANOVA) on critical task variables to determine if there were any trends consistent with our hypotheses. The IT group also had more self-reported mild hypoglycemic episodes than the CT group (an average of 82 vs. 59 episodes reported during the course of the study). Glycemic control was measured every 3 months by determination of the total GHb by affinity chromatography (Glycotest II; Pierce, Rockford, IL). Subjects in the IT group had lower GHb levels during their participation in the study than those in the CT group (8.26 vs. 9.96%) ($F[1,22] = 6.99$, $P = .015$). The three groups (IT, CT, and nondiabetic) were similar in their demographic characteristics (Table 1).

Table 1—*Clinical and demographic variables at time of testing*

	Nondiabetic control subjects	CT subjects	IT subjects
n	16	12	13
Age (years)	14.7 ± 2.8	14.3 ± 2.7	13.9 ± 2.8
WISC-III Vocabulary (scaled score)	11.5 ± 2.5	11.2 ± 2.1	11.6 ± 2.9
WISC-III Block Design (scaled score)	11.3 ± 2.6	10.8 ± 2.9	11.4 ± 3.5
Parent level of education (years)	15.1 ± 2.6	13.8 ± 2.1	14.6 ± 2.3
Age at onset (years)	—	11.9 ± 2.8	11.7 ± 2.8
Duration of disease at time of testing (years)	—	2.4 ± 0.5	2.2 ± 0.7
Severe hypoglycemic episodes per 100 patient-years	—	28	85

Data are n or means ± SD.

Procedure

Type 1 diabetic patients' glucose levels were measured to determine that they were not hypoglycemic (<70 mg/dl) before beginning the testing. Participants were then given a 2-h battery of tests to assess memory, motor speed, response inhibition, and general intelligence by a single trained experimenter (N.B.). Rest periods were provided as necessary.

Memory

Spatial Delayed Response task. This task has been previously described (26). Children were required to focus on a central fixation point on a computer screen. While they remained fixated, a cue appeared in 1 of 32 possible locations for 150 ms. A delay was then imposed for 5 or 60 s. During these delays, children performed an attention task requiring them to respond whenever they saw a diamond shape appear in the center of the screen. After the delay, children were required to point to the place on the computer screen where they remembered seeing the cue. Responses were measured in x and y coordinates and compared with the actual location of the cue. A total of 24 experimental trials were presented, 8 trials at each delay plus 8 "cue-present" trials that did not require memory for the location of the cue. Mean error (distance from the target) was calculated for each child for each type of trial

(5 s, 60 s, and cue present). This task was used to measure subjects' spatial short-term memory at short delays and spatial long-term memory at long delays. Medial temporal dysfunction is associated with poor memory on long delays (19,26,27). Average test–retest reliability for the delay conditions on this task is 0.88 (T.H., unpublished observations).

Delayed Match to Sample List

Presentation task. Children were seated in front of a computer monitor and given three conditions, each with the same basic structure but differing in the stimuli used and in the delay imposed. First, children were shown 30 abstract patterns in groups of three. Each group of three was presented for 10 s. Children were instructed to memorize the patterns. After these study trials, either no delay occurred (condition 1) or a delay period of 4 min occurred (conditions 2 and 3). In condition 3, children were shown an additional 30 stimuli in groups of three during the delay. The children then received 10 recognition trials. Each recognition trial consisted of three patterns shown simultaneously for 10 s. The children were instructed to indicate which one of the patterns had been shown in the presentation trials. Only 10 of the 30 originally presented stimuli were tested in the recognition phase. In condition 3, the stimuli in the second set of 30 were not tested because they simply served as a distractor task. The computer recorded responses and response times. The order of conditions was counterbalanced across children to minimize any order effects on performance. This task assesses pattern learning and recognition. Adult animals with medial temporal lobe damage perform poorly on similar tasks (28).

Word Recognition task. This task tested the ability to recognize orally presented words and was designed to approximate the Delayed Match To Sample List Presentation (DMSL) task. First, children were presented with 30 tape-recorded words one at a time and were instructed to memorize the words. After hearing these words, either no delay occurred (condition 1) or a delay period of 50 s occurred (conditions 2 and 3). In condition 3, the children were given an extra 30 words for memorization. The children were then given 10 recognition trials where they were asked, "Was it word 1, word 2, or word 3?" Children were asked to say the word that they recognized. Words were controlled for age of acquisition, imagery, familiarity, and concreteness (29,30). The order of conditions was counterbalanced across children to minimize any order effects on performance. This task assesses verbal learning and recognition.

Paragraph Recall task. The details of this task have been previously described (26). An audiotape recording of two short stories was played for the children. Children were asked to recall each narrative twice, immediately after the presentation and after a delay of ~70 min. Responses were recorded, transcribed, and scored. This task assesses verbal immediate and delayed declarative memory. After medial temporal damage, performance on the delayed recall trial is generally impaired (31).

Spatial and Object Memory task. This task is based on Smith and Milner's spatial and object memory task (32,33). Participants were shown an array of 16 toy objects and asked to name them and estimate their price. After a delay, participants were asked to name the objects from memory. They were then given the objects and asked to place them in their original locations. Thus, there is an immediate and delayed free recall for object names and for spatial locations. Verbal and spatial responses were recorded. This task assesses spatial and object declarative memory. Performance on this test is sensitive to right medial temporal damage.

Motor speed and inhibition

Grooved Pegboard task. This task was administered during the 4-min delay in condition 3 of the DMSL task and measures fine motor control and speed. Children were asked to place notched pegs into a pegboard as quickly as possible. The task was first performed with the dominant hand and then with the nondominant hand. Total time to complete the board was recorded for each hand. Impairment in these skills has been associated with early-onset type 1 diabetes (3).

Response Inhibition task. This task has been previously described in detail (26). Children were shown 30 trials in which a small block of color appeared randomly on a computer screen, and then the children were asked to name the color. The children were then shown 60 trials in which a block of color of the same size was in the center of a larger block of color and were again asked to name the color of the small block. On half of the trials, both blocks were the same color; on the other half of the trials, the blocks were different colors, which required the children to inhibit their response to the larger, more prominent color. Voice-onset times and accuracy were recorded and compared between conditions. Similar tasks have been shown to be sensitive to frontal lobe dysfunction and require response inhibition (34).

General intelligence

Vocabulary and Block Design task. These tasks were given as a measure of general cognitive functioning to the nondiabetic comparison group only. Type 1 diabetic patients had previously received the entire Wechsler Intelligence Scale for Children, third revised edition (WISC-III) (35) battery on entry to the larger study from which they were recruited.

Statistical analysis

Results are means ± SD unless otherwise specified. Repeated-measures general linear models analyses were performed on tasks with more than one condition, with group (IT, CT, and control) as the independent variable. Significant effects ($P < 0.05$) were followed up with ANOVAs and/or *t* tests.

RESULTS

Memory

Spatial Delayed Response task. A significant interaction between condition and group was detected ($F[4, 35] = 3.70$, $P = 0.01$). Post hoc *t* tests revealed a significant difference ($P = 0.05$) between the IT group and the CT and control groups for the longest delay only (60 s), which indicates impaired spatial long-term memory (Fig. 1). No difference was found between groups on the sustained attention task performed during the delays (accuracy, $F[2, 30] = 0.78$, $P = 0.47$; reaction time, $F[2, 30] = 0.27$, $P = 0.77$).

In addition, we compared the children who experienced severe hypoglycemic episodes with age-matched type 1 diabetic children who did not experience any severe episodes and nondiabetic subjects. The hypoglycemia group performed more poorly on the 60-s delay condition than the other two groups, but this effect was not significant due to large variability and limited sample sizes ($F[4, 30] = 1.69$, $P = 0.198$).

DMSL

Accuracy task. Performance was significantly worse on condition 3 compared with both conditions 1 and 2 ($F[2, 70] = 8.37$, $P = 0.001$) for all groups. The effect of

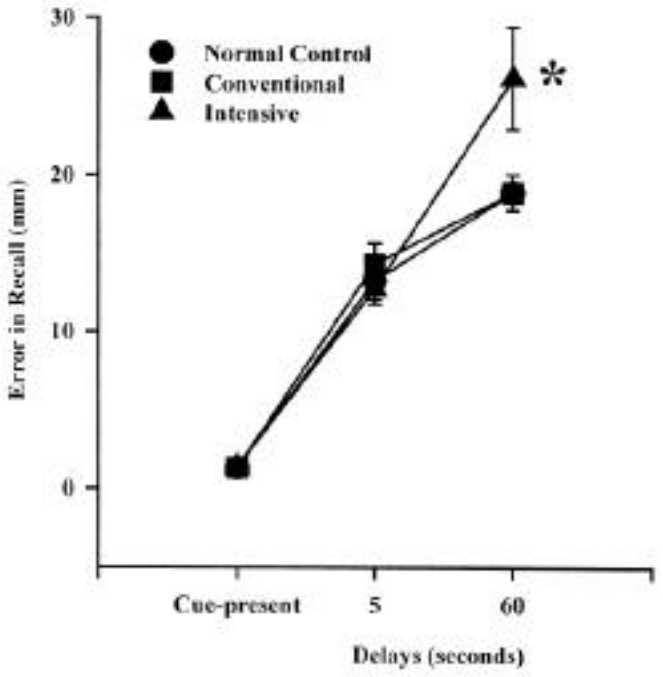

Figure 1—*SDR error (mean ± SD) for each condition by each group. *A significant difference (P = 0.05) between the type 1 diabetic IT group and the other two groups.*

group and the interaction between group and condition were not significant (Table 2).

Median Response Time task. Significant main effects of condition and group were found. Reaction time was longer on condition 3 versus condition 2 for all subjects (data not shown) ($F[2, 70] = 3.86$, $P = 0.03$). The IT group performed significantly slower overall than the other two groups ($F[2, 35] = 4.90$, $P = 0.01$) (Fig. 2).

Word Recognition task. All subjects performed better on condition 1 and condition 2 than on condition 3 ($F[2, 72] = 9.43$, $P < 0.001$). The effect of group and the interaction between group and condition were not significant (Table 2).

Paragraph Recall task. For all subjects, performance was poorer on delayed recall than on immediate recall ($F[1, 35] = 33.8$, $P < 0.001$). The effect of group and the interaction between group and condition were not significant (Table 2).

Spatial and Object Memory task. Delayed object recall was worse than immediate recall for all subjects ($F[1, 36] = 66.94$, $P <$

Table 2—*Values for each task and condition*

	Nondiabetic control subjects	CT subjects	IT subjects
n	16	12	13
DMSL Accuracy task (% correct; chance = 33%)			
Condition 1	57 ± 19	52 ± 20	55 ± 23
Condition 2	48 ± 20	51 ± 21	59 ± 25
Condition 3	46 ± 13	40 ± 19	39 ± 11
Word Recognition task (number of words recognized)			
Condition 1	8.4 ± 1.3	8.1 ± 1.8	8.5 ± 1.3
Condition 2	7.4 ± 2.0	8.3 ± 1.6	8.5 ± 1.3
Condition 3	6.9 ± 1.4	6.8 ± 1.5	7.5 ± 1.8
Paragraph Recall task (bits recalled)			
Immediate	10.3 ± 3.0	9.6 ± 1.4	10.6 ± 2.7
Delayed	5.6 ± 3.6	7.3 ± 1.2	8.7 ± 2.3
Spatial and Object Memory task — Object Recall (number of objects recalled)			
Immediate	8.8 ± 1.9	8.7 ± 2.4	8.7 ± 2.2
Delayed	11.3 ± 2.4	11.6 ± 1.6	11.2 ± 2.4
Spatial and Object Memory task — Spatial Recall (centimeters of displacement)			
Immediate	2.2 ± 1.6	3.1 ± 3.7	2.5 ± 3.7
Delayed	2.8 ± 2.1	3.4 ± 2.6	1.8 ± 1.1
Response Inhibition — Median Reaction Time task (m)			
Condition 1	609 ± 60	594 ± 41	641 ± 109
Condition 2	663 ± 65	641 ± 42	671 ± 105
Condition 3	713 ± 78	700 ± 59	706 ± 112
Response Inhibition — Accuracy task (% correct)			
Condition 1	99 ± 1	100 ± 0	99 ± 1
Condition 2	99 ± 2	99 ± 1	99 ± 2
Condition 3	99 ± 2	98 ± 3	98 ± 4

Data are means or medians ± SD.

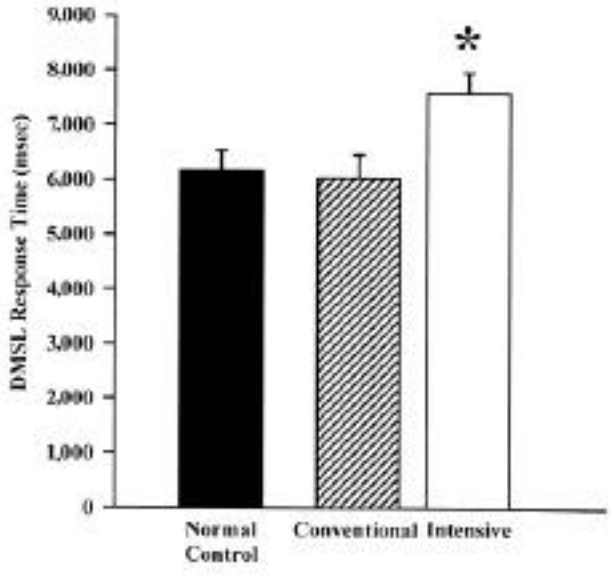

Figure 2—*DMSL reaction time (median ± SD) collapsed across conditions for each group. *A significant difference (*P *< 0.01) between the type 1 diabetic IT group and the other two groups.*

0.001). No other significant effects were found (Table 2).

Motor speed and inhibition

Grooved Pegboard task. As expected, performance was faster overall with the dominant hand ($F[1, 35] = 37.77$, $P < 0.001$). In addition, both diabetes groups (IT and CT) were significantly slower than the control group overall ($F[2, 35] = 3.93$, $P = 0.03$) (Fig. 3).

Response Inhibition

Accuracy task. All subjects performed more accurately on condition 1 compared with conditions 2 and 3 and more accurately on condition 2 than condition 3 ($F[2, 70] = 3.65$, $P = .03$). The effect of group and the interaction between group and condition were not significant (Table 2).

Median Reaction Time task. All subjects performed more slowly on conditions 2 and 3 than on condition 1 and more slowly on condition 3 than condition 2 ($F[2, 70] = 98.8$, $P < 0.001$). The effect of group and the interaction between group and condition were not significant (Table 2).

General intelligence

Vocabulary and Block Design task. There were no differences between groups on these measures of general intelligence ($P > 0.85$) (Table 1).

CONCLUSIONS

The results of this study showed that children with type 1 diabetes on IT had a three times greater risk of severe hypoglycemia. The IT group also had impaired memory performance on a sensitive measure of spatial long-term memory (Spatial Delayed Response [SDR]) compared with the CT group and the nondiabetic group. In addition, children in the IT group had relatively slow response times on a pattern memory task (DMSL). Finally, both groups of type 1 diabetic children were significantly impaired on a fine motor control and motor speed task (Grooved Pegboard) compared with their peers without type 1 diabetes. These results in part support our hypothesis that children with a higher risk of severe hypoglycemia are relatively impaired on sensitive tests of delayed declarative memory. However, these children were impaired on only one of several declarative memory tasks. This finding suggests that there may be some relatively restricted risk of severe hypoglycemia in children with a later age of onset (aged >5 years), although this relationship was only indirectly assessed in this study. These results also raise some methodological and theoretical questions.

Memory

The relative impairment on the long delay condition of the SDR task in the IT group is similar to previously reported findings in children (aged 7–16 years) and adults with left or right temporal lobe epilepsy (26,36). The IT group performed 30% worse than the CT group or control subjects on the long delay, the pediatric epilepsy group performed 40–45% worse than control subjects on the same long delay, and the adult epilepsy group performed 37% worse than control subjects on a longer delay (120 s).

Although it is possible that this pattern is related to general visuospatial impairment, this explanation seems unlikely for several reasons. First, the IT group performed poorly only on long delays, not the short delays of the SDR task. Second, a previous study (4) showed that type 1 diabetic patients with an early age of onset and a history of severe hypoglycemia performed adequately on spatial tasks without memory demands. This finding is also unlikely

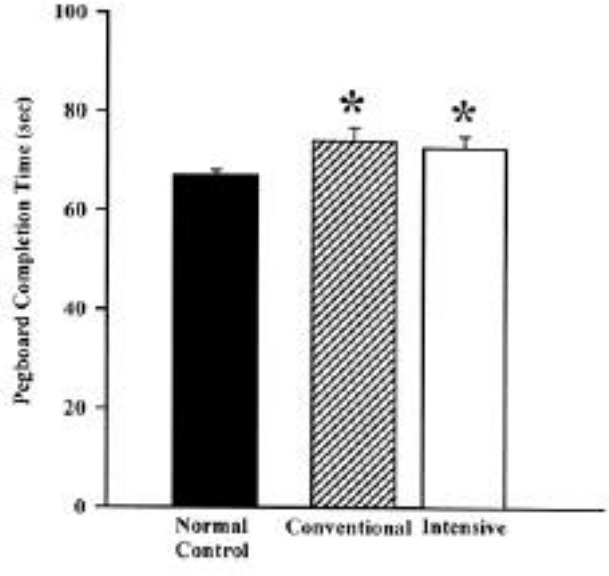

Figure 3—*Grooved Pegboard completion times (mean ± SD) collapsed across hands for each group. *A significant difference (*P *< 0.05) between the two type 1 diabetic groups and the control group.*

to be explained by differences between groups in visual attention skills. First, the groups did not differ in sustained attention performance during the delays of the SDR task, which is consistent with the findings of Rovet and Alvarez (37). Second, although other studies have reported impairment in specific types of attention associated with a history of hypoglycemic seizures (37), there is no reason to expect that these impairments would interfere preferentially with the long delay condition of the SDR task. Finally, the groups did not differ in their accuracy on tasks with a much higher demand on visual attention (DMSL).

Interestingly, children with temporal lobe epilepsy showed a similar pattern of performance on the SDR task (26). In addition, these children did not show deficits on Story Recall or a task similar to the DMSL task. Thus, our IT group performed in a manner similar to a group of children with known temporal lobe dysfunction not only in terms of which tasks indicated impairments but also in terms of the tasks on which they were not impaired. The fact that a group of children with known temporal lobe dysfunction performed similarly to children with type 1 diabetic undergoing IT may indicate that similar mechanisms could explain both groups' performances.

It should be noted that the level of impairment of the IT group on the SDR task, although statistically significant, may not cause any noticeable difficulty with daily functioning. However, this relative impairment could be the beginning of a potential cumulative effect of IT or severe hypoglycemia on memory performance. After decades of type 1 diabetes and repeated severe hypoglycemic episodes, this impairment may become more noticeable on clinical memory tests (4) and could affect daily functioning. Careful longitudinal studies are needed to test this hypothesis adequately.

Motor speed

The response speed impairment found in IT patients on the DMSL task could be related to difficulty in pattern recognition. IT patients may take longer to inspect each option and match it to the memorized pattern, perhaps because their memory of the patterns is less salient. However, in that case, we would have expected some decrease in the accuracy of performance as well, and this was not the case. Interestingly, on a similar pattern recognition task, slowed response time was found in adults with temporal lobe epilepsy (36). Alternatively, IT patients may be slower to respond to any difficult task. This group did not have distinct reaction time slowing on a voice reaction time task; however, this task was also relatively easy (performance accuracy was ≥98% on all conditions). Further investigation is needed to determine the true nature of this impairment.

Children with type 1 diabetes, regardless of treatment group, were slower on a test of fine motor speed and coordination (Grooved Pegboard) than children without type 1 diabetes. Slowed motor speed is a common finding in type 1 diabetes and has also been related to early onset of the disease and lower blood glucose levels (3,5,15,38). However, type 1 diabetic subjects were not hypoglycemic before undergoing testing, and we found no correlation between blood glucose levels at time of testing and motor speed in the type 1 diabetic group ($P > 0.50$).

Summary

In conclusion, these results suggest that some memory impairment may be associated with IT that is consistent with the effects of severe hypoglycemia (4) and medial temporal damage or dysfunction (19,21,23,24,39). Although these patients did not show impairment on all of the declarative memory tasks administered, a similar pattern of performance has been reported in children with known temporal lobe dysfunction, which supports the validity of these results. The issue of cognitive risk due to severe hypoglycemia in children with type 1 diabetes is important enough to warrant further consideration of these findings. Only through further study of this issue can any strong conclusions be drawn. By following a larger group of type 1 diabetic children longitudinally, we may be able to determine whether a direct relationship exists between severe hypoglycemia and cumulative risk to memory and other skills. Such a finding may have significant consequences for the treatment of children and adolescents with type 1 diabetes. For example, it may be necessary to be especially cautious in imposing overly strict standards for glucose control in young patients with type 1 diabetes because of the increased risk of hypoglycemia associated with IT regimens (25), particularly for adolescents (40,41).

Based at least in part on the results of the DCCT (42), it has been assumed that the increased risk of severe hypoglycemia observed during IT in type 1 diabetes in teenagers and young adults is not associated with permanent cognitive deficits. However, our results suggest that it is important to test this conclusion more rigorously, particularly in larger groups of children and adolescents, by using prospective measurement of hypoglycemia and sensitive memory tasks. If such an effect is confirmed, the risk of IT for younger patients could be greater than is generally accepted (43,44) because IT may increase the risk of memory impairment in these children. On the other hand, IT has many clearly demonstrated benefits for patients with type 1 diabetes (45,46). Without a clear demonstration of the relationship between severe hypoglycemia and memory deficits in children with type 1 diabetes on an IT regimen, withholding or modifying this treatment based only on the available data is unfounded.

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