Frequency and Timing of Severe Hypoglycemia Affects Spatial Memory in Children With Type 1 Diabetes

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OBJECTIVE — Repeated severe hypoglycemia has been reported to reduce long-term spatial memory in children with type 1 diabetes. Early exposure to hypoglycemia may be more damaging to cognitive function than later exposure. Our goal was to determine whether the age at which severe hypoglycemia occurs modulates the impact of severe hypoglycemia frequency on long-term spatial memory.

RESEARCH DESIGN AND METHODS — We combined data from three independent studies to obtain a sample of children aged 6–18 years with type 1 diabetes (n = 103) and nondiabetic control subjects (n = 60). Each study evaluated previous severe hypoglycemia and tested short (5 s)- and long (60 s)-delay spatial memory with the spatial delayed response task. Type 1 diabetic participants were categorized as having zero, one to two, or three or more severe hypoglycemic episodes and as having their first severe hypoglycemic episode before or after 5 years of age. Information on chronic hyperglycemia (HbA1c values) was also collected.

RESULTS — We found that repeated severe hypoglycemia (more than three episodes) reduced long-delay spatial delayed response performance, particularly when severe hypoglycemic episodes began before the age of 5 years. Age of type 1 diabetes onset and estimates of chronic hyperglycemia did not influence performance.

CONCLUSIONS — High frequency of and early exposure to severe hypoglycemia during development negatively affects spatial long-term memory performance.

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Severe hypoglycemia is a significant and relatively common complication of insulin treatment in children with type 1 diabetes (1). The long-term cognitive effects of such episodes have been debated. One hypothesis is that severe hypoglycemia occurring early in development is more harmful to cognitive function than severe hypoglycemia later in development, but few data address this issue directly. If this hypothesis was correct, it could explain the consistent finding that early onset of type 1 diabetes predicts poorer cognitive function (2–5). Since only individuals with early onset of diabetes would be expected to experience early severe hypoglycemia, age of onset can be confounded with the age of first severe hypoglycemia. Although previous studies (6,7) have examined the impact of age of onset and of severe hypoglycemia history on cognitive function in children, none have established whether the age at which severe hypoglycemia occurs is important in determining cognitive outcome. It is possible that severe hypoglycemia frequency and timing are both important contributors to cognitive dysfunction in children with type 1 diabetes.

We combined data from three studies, all of which found that severe hypoglycemia preferentially decreased spatial long-term memory in children with type 1 diabetes (8,9). We used these data to determine how the effects of severe hypoglycemia on spatial memory were modulated by the age at which severe hypoglycemia occurred. Further, we wanted to determine whether exposure to chronic hyperglycemia contributed to these results on spatial memory (10,11). Our goal was not to survey all possible cognitive effects of severe hypoglycemia but rather to use a previously established effect of severe hypoglycemia frequency on memory to determine whether other clinical variables modulate this effect. We hypothesized that early severe hypoglycemia (before 5 years of age) would have a more deleterious effect than later severe hypoglycemia (after age 5 years) on spatial memory due to the vulnerability of developing skills and their underlying neural systems.

RESEARCH DESIGN AND METHODS — Data were combined from three independent studies spanning 13 years. Results from two (8,9) of three studies have been published separately. All three studies used similar procedures. Type 1 diabetic children were drawn from the same clinic at St. Louis Children’s Hospital, Washington University School of Medicine in St. Louis. All protocols were approved by the Washington University School of Medicine’s Human Subjects Committee, and all participants and their guardians signed informed consents.

For all studies, children with type 1 diabetes and nondiabetic control subjects were tested. Patients were excluded for a history of diabetic retinopathy, nephropathy, or neuropathy. Subjects were excluded for mental retardation, enrollment in special education classes, known major mental illness, significant neurological history not due to diabetes, taking medications with known central nervous system effects, or physical limitations that would interfere with testing.
Study 1
Subjects in study 1 (9) were type 1 diabetic (n = 24) and nondiabetic control (n = 16) subjects ranging from 9 to 18 years of age. Type 1 diabetic patients were recruited from a larger study in which children aged 6–16 years at diagnosis were randomized at the time of diagnosis to either intensive diabetes therapy or conventional diabetes therapy. Subjects were tested after ~18 months of treatment. Control subjects were recruited from the general community and included some siblings or friends of type 1 diabetic children.

Study 2
Subjects in study 2 (8) were type 1 diabetic (n = 35) and nondiabetic sibling control (n = 22) subjects ranging between 6 and 16 years old. Type 1 diabetic patients were recruited from a larger treatment study in which all had type 1 diabetes for at least 2 years or were diagnosed for at least 1 year with negligible stimulated C-peptide at study entry. Subjects were tested at study entry.

Study 3
Subjects in study 3 were type 1 diabetic (n = 45) and nondiabetic sibling control (n = 22) subjects and were between 6 and 16 years old. Patients all had type 1 diabetes for at least 2 years before entry into the study.

Ascertainment of glycemic history
Type 1 diabetic patients' history of severe hypoglycemia, including the age of each event, was determined through parental report and chart review. In study 1, this information was obtained prospectively, and in studies 2 and 3 it was retrospective. Severe hypoglycemia was defined as events with severe neurological dysfunction, such as seizure, loss of consciousness or inability to arouse from sleep, and/or those that required assistance of someone other than the patient for treatment. Treatment could be given in the form of sugar and food, a glucagon injection, or intravenous glucose. In addition, all available HbA1c (A1C) levels from diagnosis to testing were acquired from medical charts.

Testing procedures
For all studies, a 2-h battery of cognitive measures was administered. The battery always included the spatial delayed response task and verbal and nonverbal intelligence measures (study 1: vocabulary and block design from the Wechsler Intelligence Scale for Children 3rd Edition [12], study 2: verbal–spatial relations and nonverbal matrices from the Das–Naglieri Cognitive Assessment Systems Battery [13], study 3: general information and spatial relations from the Woodcock–Johnson III [14]). Results from measures unique to each study have been reported elsewhere (8, 9). Blood glucose levels were ascertained before testing in type 1 diabetic subjects. If the reading was low (<60 mg/dl) or symptoms were reported, a snack or lunch was given. Testing began once euglycemia was achieved. These situations happened very infrequently (zero to two times in each study group).

Spatial delayed response task
This task has been used extensively for assessing spatial short- and long-term memory. Details and illustrations of the procedure have been reported elsewhere (9, 15, 16). Short delays require short-term memory and intact dorsolateral prefrontal function (17–20), whereas long delays require long-term memory and intact medial temporal function (21–28). Subjects sat in front of a computer monitor. On each trial, they focused on a cross in the center of the screen. A dot appeared briefly (150 ms) in 1 of 32 locations at a fixed radius from the center of the screen and then disappeared. A delay was then imposed of 5 or 60 s. During the delay, subjects observed shapes (triangle, diamond, or square) one at a time in random order in the center of the screen. Subjects had to press a button every time they saw the diamond shape. After the delay, the cross reappeared in the center of the screen and subjects were required to point to the location on the screen where they remembered seeing the dot for that trial. The distance between the original location of the dot and the remembered location was calculated (error in millimeters). On some trials, the dot returned to the screen after the delay and subjects had to place their finger on the dot (cue present trials). Trials were presented in random order, with eight trials at each delay condition (5 and 60 s) and four or eight cue-present trials.

Analyses
Subjects were categorized as having zero (0 group), one to two (1–2 group), or three or more (3+ group) severe hypoglycemic episodes (severe hypoglycemia frequency) and as having their first severe hypoglycemic episode before or after age 5 years (severe hypoglycemia timing). We categorized these variables for three reasons: 1) the distribution of number of reported episodes tends to be skewed, 2) previous studies suggested a dose response of severe hypoglycemia on spatial delayed response long-delay performance (8), and 3) to ensure a relatively even distribution of subjects (at least 25) within each severe hypoglycemia frequency category.

Repeated-measures general linear model analyses were performed to assess the effects of severe hypoglycemia frequency and timing, chronic hyperglycemia, and age of onset on spatial delayed response performance. The dependent variable in all analyses was error (in millimeters) on the spatial delayed response task and the repeated measure was delay (cue-present, 5 and 60 s). Independent variables depended on the subgroups being assessed. Age and age of onset were covaried from all analyses with diabetic subgroups only. In analyses including control subjects, only age was covaried. Significant main effects or interactions were followed with univariate analyses and post hoc t tests.

To determine the potential contribution of chronic hyperglycemia on spatial delayed response performance, we examined subjects' available A1C record from diagnosis to participation in the study. Subjects in our earliest study (study 1, n = 24, type 1 diabetes) had only total glycated hemoglobin levels and were not included in these analyses. Mean A1C level was calculated for each patient. However, to also take into account the duration of exposure to hyperglycemia, we multiplied each patient's percentage of A1C results >9.0% by the duration of type 1 diabetes. Correlations were performed between mean A1C, duration of exposure to hyperglycemia, and spatial delayed response performance. Hyperglycemia measures were also covaried out of models assessing the effects of severe hypoglycemia on spatial delayed response performance.

RESULTS
Subjects
The total sample consisted of 103 children with type 1 diabetes and 60 nondiabetic control subjects aged 6–18 years. Sex distributions were equivalent between nondiabetic control subjects (43% female) and children with type 1 diabetes (42% female). See Tables 1 and 2 for de-
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Table 1—Demographic and clinical variables across severe hypoglycemia

<table>
<thead>
<tr>
<th>Type 1 diabetic subjects</th>
<th>0 severe hypoglycemic group</th>
<th>1–2 severe hypoglycemic group</th>
<th>3+ severe hypoglycemic group</th>
<th>Nondiabetic control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>40</td>
<td>38</td>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>Age (years)</td>
<td>13.4 ± 2.8*</td>
<td>12.8 ± 2.2</td>
<td>12.0 ± 2.5†</td>
<td>12.8 ± 3.0</td>
</tr>
<tr>
<td>Age of onset (years)</td>
<td>10.2 ± 3.6*§§</td>
<td>8.0 ± 2.7*†</td>
<td>5.7 ± 3.7†§</td>
<td>—</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>3.3 ± 1.6*§§</td>
<td>4.8 ± 2.4*†</td>
<td>6.3 ± 3.2†§</td>
<td>—</td>
</tr>
<tr>
<td>Parents’ education (years)</td>
<td>14.1 ± 2.4§§</td>
<td>14.7 ± 2.1</td>
<td>14.4 ± 2.0</td>
<td>15.0 ± 2.2†</td>
</tr>
<tr>
<td>Nonverbal intelligence (standard score)</td>
<td>103.7 ± 12.6</td>
<td>106.6 ± 11.7</td>
<td>106.6 ± 16.9</td>
<td>106.4 ± 11.1</td>
</tr>
<tr>
<td>Verbal intelligence (standard score)</td>
<td>106.3 ± 14.8</td>
<td>108.0 ± 9.6</td>
<td>106.9 ± 12.6</td>
<td>108.0 ± 12.4</td>
</tr>
<tr>
<td>Number of severe hypoglycemic episodes</td>
<td>0</td>
<td>1.2 ± 0.5*</td>
<td>6.6 ± 9.4‡</td>
<td>—</td>
</tr>
<tr>
<td>Number of seizures during severe hypoglycemic episodes</td>
<td>0</td>
<td>1.8 ± 0.4*</td>
<td>1.3 ± 0.5</td>
<td>—</td>
</tr>
<tr>
<td>Mean A1C (%)</td>
<td>8.1 ± 1.1*</td>
<td>8.4 ± 0.7*</td>
<td>8.9 ± 0.9†‡</td>
<td>—</td>
</tr>
<tr>
<td>Estimated duration of exposure to hypoglycemia (years)</td>
<td>0.8 ± 1.1*</td>
<td>1.3 ± 1.5*</td>
<td>2.7 ± 2.3†‡</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are means ± SD. Frequency subgroups and nondiabetic control subjects. Spatial delayed response error is adjusted for age and age of onset for type 1 diabetic subgroups and adjusted for age for nondiabetic control subjects. *Different from 3+ severe hypoglycemic group, P < 0.05; †different from 0 severe hypoglycemic group, P < 0.05; ‡different from 1–2 severe hypoglycemic group, P < 0.05; §different from nondiabetic control subjects, P < 0.05.

Severe hypoglycemia frequency

As expected, we found a significant interaction between severe hypoglycemia frequency and delay on spatial delayed response performance [F(4, 194) = 6.2, P < 0.001]. At the long delay, the 3+ severe hypoglycemic subgroup performed worse than the other two subgroups (zero and one to two episodes) [F(2, 97) = 5.8, P = 0.0044] and nondiabetic control subjects [F(3, 157) = 3.7, P = 0.01]. In contrast, there were no differences between groups on the cuepresent or short (5-s)-delay conditions (PS > 0.75) (Fig. 1A). There were also significant main effects of delay [F(2, 194) = 64.9, P < 0.001] and severe hypoglycemia frequency [F(2, 97) = 3.2, P = 0.045].

Severe hypoglycemia frequency and timing

We found a significant three-way interaction between delay, severe hypoglycemia frequency, and timing [F(2, 114) = 4.5, P = 0.01]. Children with more than three episodes of severe hypoglycemia and early first severe hypoglycemia (aged <5 years) performed worse than all other subgroups, including control subjects [F(10, 310) = 3.63, P < 0.001] (Fig. 1B). In addition, there were significant main effects of delay [F(2, 114) = 39.3, P < 0.001] and severe hypoglycemia frequency [F(1, 57) = 6.7, P = 0.01], significant interactions between delay and severe hypoglycemia frequency [F(2, 114) = 13.2, P < 0.001], and between delay and severe hypoglycemia timing [F(2, 114) = 3.35, P = 0.039]. Although there appear to be more episodes of severe hypoglycemia in the 3+ early group compared with the 3+ late group, this result was not statistically significant (Table 2).

One subject in the 3+ early group experienced 50 episodes. Removing the subject from the analysis did not alter the effect of severe hypoglycemia frequency and timing on memory performance.

There were 22 type 1 diabetic sub-

Table 2—Clinical and demographic variables across severe hypoglycemia frequency and timing type 1 diabetic subgroups

<table>
<thead>
<tr>
<th>Type 1 diabetic subgroups</th>
<th>1–2 early severe hypoglycemic group</th>
<th>1–2 late severe hypoglycemic group</th>
<th>3+ early severe hypoglycemic group</th>
<th>3+ late severe hypoglycemic group</th>
<th>Nondiabetic control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>4</td>
<td>34</td>
<td>9</td>
<td>16</td>
<td>60</td>
</tr>
<tr>
<td>Age (years)</td>
<td>10.3 ± 2.8*†</td>
<td>13.2 ± 2.0*‡§</td>
<td>10.3 ± 2.7*†§</td>
<td>12.5 ± 2.3*§</td>
<td>12.8 ± 3.0§</td>
</tr>
<tr>
<td>Age of onset (years)</td>
<td>3.4 ± 1.3*††</td>
<td>8.6 ± 2.3*‡§</td>
<td>1.8 ± 1.0*†</td>
<td>7.9 ± 2.7*‡§</td>
<td>—</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>6.9 ± 3.3</td>
<td>4.6 ± 2.2*†</td>
<td>8.5 ± 2.5†</td>
<td>5.1 ± 2.2*†§</td>
<td>—</td>
</tr>
<tr>
<td>Number of severe hypoglycemic episodes</td>
<td>1.0 ± 0.0</td>
<td>1.3 ± 0.5</td>
<td>9.9 ± 15.2†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of seizures during severe hypoglycemic episodes</td>
<td>1.8 ± 0.5</td>
<td>1.8 ± 0.4</td>
<td>1.2 ± 0.4</td>
<td>1.3 ± 0.5</td>
<td>—</td>
</tr>
<tr>
<td>Age of first severe hypoglycemic episode (years)</td>
<td>3.8 ± 0.6*†</td>
<td>10.9 ± 2.6*‡§</td>
<td>2.7 ± 1.2*†</td>
<td>9.1 ± 2.2*‡§</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are means ± SD. Spatial delayed response error is adjusted for age and age of onset for type 1 diabetic subgroups and adjusted for age for nondiabetic control subjects. *Different from 1–2 late severe hypoglycemic group, P < 0.05; †different from 3+ late severe hypoglycemic group, P < 0.05; ‡different from 1–2 early severe hypoglycemic group, P < 0.05; §different from 3+ early severe hypoglycemic group, P < 0.05; ¶different from nondiabetic control subjects, P < 0.05; ||without one outlier, 4.9 ± 2.5.
jecs with early onset (before age 5 years) and 81 with later onset (after age 5 years).

In a similar analysis, we did not find a significant interaction between delay, severe hypoglycemia frequency, and age of onset or a significant main effect of age of onset ($P = 0.67$) on spatial delayed response. The interaction between severe hypoglycemia frequency and age of onset was significant [$F(2, 95) = 3.3, P = 0.04$], but the direction of the effect was inconsistent across subgroups. Specifically, within the 0 and 1–2 severe hypoglycemic subgroups, early age of onset was associated with better performance than later age of onset; within the 3+ subgroup, early age of onset was associated with worse performance than later onset. However, none of these comparisons were significant.

Due to concerns that age at testing could influence the interaction between severe hypoglycemia frequency and timing, we reexamined our sample after restricting the subject pool to children between 9 and 15 years of age, an age range that was well represented across subgroups. This restriction eliminated six subjects overall. With this restriction, there was no significant effect of subgroup on age [$F(3, 57) = 1.2, P = 0.31$]. However, there was still a significant interaction between delay, severe hypoglycemia frequency, and timing on spatial delayed response performance [$F(2, 174) = 5.7, P = 0.004$] with the 3+ early severe hypoglycemic group performing worse than all other subgroups, including the non-diabetic control subjects ($P < 0.05$).

**Seizure frequency and timing**

Thirty-six type 1 diabetic children had one or more seizures during severe hypoglycemia. Ten of these had three or more seizures. No significant effects of seizure frequency category (zero, one to two, or three or more episodes) or seizure timing (before age 5 vs. after age 5) or interactions were found on spatial delayed response ($PS > 0.09$).

**Chronic hyperglycemia**

A1C levels were available on the 79 subjects from studies 2 and 3. There was an average of $12.1 \pm 5.7$ A1C readings total and $2.6 \pm 1$ A1C levels per year obtained for each subject. Mean A1C and duration of exposure to hyperglycemia differed significantly between severe hypoglycemia frequency categories [mean A1C, $F(2, 76) = 5.6, P = 0.006$; duration of exposure to hyperglycemia, $F(2, 76) = 7.9, P = 0.001$] (Table 1). Neither measure correlated significantly with short- or long-delay spatial delayed response performance across all type 1 diabetic subjects (all $PS > 0.15$) nor within each severe hypoglycemia frequency category. In addition, the 3+ early severe hypoglycemic group was not significantly different from the 3+ late severe hypoglycemic group in mean A1C or duration of exposure to hyperglycemia ($PS > 0.11$).

After covarying chronic hyperglycemia measures, severe hypoglycemia frequency and timing still had a significant interaction with delay on long-delay spatial delayed response performance [mean A1C, $F(2, 100) = 4.78, P = 0.01$; duration of exposure to hyperglycemia, $F(2, 100) = 4.35, P = 0.02$].

**CONCLUSIONS**

Results of these analyses confirmed that repeated severe hypoglycemia reduces long-delay spatial memory performance on a spatial delayed response test. We then used this effect to demonstrate novel support for the hypothesis that repeated severe hypoglycemia starting before age 5 years may be harmful to long-term memory functioning. We also found that estimates of chronic hyperglycemia do not contribute to this relationship. We suggest that the developing brain of very young children may be more vulnerable than the brain of older children to the negative effects of severe hypoglycemia on longer-term spatial memory. However, these findings do not rule out the possibility that more frequent or profound severe hypoglycemia after age 5 years could also negatively affect memory function. Indeed, a prior study (29) suggests that it does. Further, we found no evidence to suggest that occasional seizures during hypoglycemia were primarily responsible for changes in memory performance, although we cannot rule out an effect of more significant exposure to seizures. It remains to be determined whether other features of severe hypoglycemia (e.g., duration, severity) or less-severe glucose fluctuations contribute to these effects.

It is reasonable to hypothesize that severe hypoglycemia may have more impact on long-term memory during early childhood when underlying neural systems are
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still developing. Neuropathological evidence from animals suggests that severe hypoglycemia preferentially harms neurons in the medial temporal region, including the hippocampus (30–33). Damage to the hippocampus in early development via early-onset temporal lobe epilepsy increases impairment on long-delay memory tasks (34). The hypothesized mechanism of this effect is disruption of normal development in the connections between the hippocampus/medial temporal cortex and prefrontal cortical areas that contribute to long-term memory (35).

Data relevant to this question in type 1 diabetes are scarce. The best suggestion of such an effect comes from the consistently reported negative effect of age of onset on various cognitive functions in type 1 diabetes. Typically, early age of onset is defined as <5 years of age and has been associated with lower function in a variety of cognitive domains (2–5). The novel data presented herein suggest that early onset of type 1 diabetes is harmful to memory primarily because it permits the possibility of experiencing severe hypoglycemia early in childhood, when more active brain development takes place.

Hyperglycemia did not appear to modulate the effect of severe hypoglycemia on long-delay spatial delayed response. We found that A1C levels over the duration of type 1 diabetes do not predict spatial delayed response performance. However, these data do not rule out the possibility that chronic hyperglycemia affects brain structure or function in ways not measured here, as suggested in some (36–41) but not all (42–45) studies on this topic.

The strengths of this study include a hypothesis-driven focused approach that allowed us to dissect the impact of relevant clinical variables on reliable cognitive effect. Weaknesses of the study include the retrospective nature of the study (e.g., no baseline data), limitations of using lifetime average A1Cs to assess overall diabetes control, and our inability to be completely precise in the number of severe hypoglycemic events or seizures experienced due to the possibility of unreported or unrecognized events. Although subjects with more hypoglycemia had longer duration of disease than those with fewer episodes, we do not feel that duration explains our differences in memory performance since age and age of onset were covariates in our analyses and duration did not correlate with performance (r = −0.01). However, with these data, we are unable to determine whether longer duration, which might result in additional episodes of severe hypoglycemia, would result in future decreases in memory performance, since patients with three or more hypoglycemic episodes had longer duration of disease than those with zero or one to two. Finally, although our total sample was larger than many previous studies, our subgroup analyses were necessarily performed on modest sample sizes. Despite these limitations, the data presented here suggest that repeated severe hypoglycemia, especially starting at an early age, is detrimental to long-term spatial memory function. Given that spatial delayed response is a simple memory task, one could speculate that the deficits seen here might be compounded in more complex or demanding spatial memory tasks. However, the relevance of these findings to other aspects of memory and learning (e.g., use of strategies, ability to benefit from repetition) or everyday spatial memory function (e.g., remembering where you put your lunchbox) are speculative and remain to be examined.

In conclusion, these data address the relative importance of both frequency and timing of severe hypoglycemia during childhood in predicting cognitive outcome in children with type 1 diabetes. Our data suggest that multiple hypoglycemic episodes beginning early in development are particularly harmful to spatial memory function. This information should be used in assessing the benefits and risks of tight glycemic control of type 1 diabetes at very young ages. However, these treatment decisions are complex and must also take into account the clear benefits of tight control in reducing complications associated with hyperglycemia, at least in adult and adolescent patients. Linking the cognitive effects seen here to changes in brain structure or function and everyday behavior would be useful in predicting the ultimate functional outcome of children with type 1 diabetes as well as in weighing the risks and benefits of treatment strategies for diabetes in childhood.

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Hershey and Associates