Gender Differences in Memory and Learning in Children with Insulin-Dependent Diabetes Mellitus (IDDM) over a 4-year Follow-up Interval

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Objective To examine demographic and disease predictors of memory and learning performance for children with diabetes and controls. Method Children with diabetes (N = 95) and demographically similar control children (N = 100) were administered the Rey Auditory Verbal Learning Test (RAVLT) initially and 4 years later. Results Unlike other groups, boys with diabetes did not make expected developmental gains on the learning trials of the RAVLT. Boys with diabetes showed a plateau in words learned from the primacy position, and girls with diabetes appeared to lose their relative gender advantage for verbal information. Longer disease duration predicted poorer learning over time. Conclusions Subtle difficulties were found in learning related to longer disease duration for a predominantly middle-class group of children with diabetes over a 4-year follow-up interval. It will be important to monitor children’s educational development to help avoid a cumulative toll on classroom performance.

Key words gender differences; cognition; diabetes.

Children with insulin-dependent diabetes mellitus (IDDM) have been shown to have mild to moderate intellectual and neuropsychological difficulties relative to children without diabetes (Holmes, O’Brien, & Greer, 1995; Northam et al., 2001; Ryan, 1988, 1999). Several factors have been found to be associated with lower performance, including male gender (Holmes, Dunlap, Chen, & Cornwell, 1992; Schoenle, Schoenle, Molinari, & Largo, 2002), lower socioeconomic status (SES; Auslander, Anderson, Bubb, Jung, & Santiago, 1990; Overstreet, Holmes, Dunlap, & Frentz, 1997), poorer metabolic control (Overstreet et al., 1997, Schoenle et al., 2002), earlier age of disease onset (Ack, Miller, & Weil, 1961; Hagen et al., 1990; Holmes & Richman, 1985; Lynch, van Schaick, Soutor, Chen, & Holmes, 2001; Rovet & Alvarez, 1997; Rovet & Ehrlich, 1999; Rovet, Ehrlich, & Hoppe, 1987, 1988; Rovet, Ehrlich, & Czuchta, 1990; Ryan, Vega, & Drash, 1985), and higher frequency and greater severity of hypoglycemic episodes (Hershey, Craft, Bhargava, & White, 1997; Rovet & Alvarez, 1997; Rovet & Ehrlich, 1999; Wolters, Yu, Hagen, & Kail, 1996). Studies of short-term memory have revealed that children with early onset diabetes use less efficient learning strategies (Hagen et al., 1990; Lynch et al., 2001) and recall fewer words (Wolters et al., 1996; Lynch et al., 2001) and that those in poorer metabolic control use less efficient learning strategies (Wolters et al., 1996).

Gender Differences in Memory and Learning

When gender differences in verbal memory and learning are examined in school-age children, boys tend to have lower verbal skills than girls (Delis, Kramer, Kaplan, & Ober, 1987; Kramer, Delis, Kaplan, O’Donnell, & Prifitera, 1997). Gender differences also have been found in children with diabetes. In general, boys tend to perform more poorly than girls on tests of verbal learning, although higher SES appears to provide some protection (Overstreet et al., 1997). School-age boys with diabetes have
been shown to have lower verbal IQ scores than other groups (Schoenle et al., 2002) and have been found to read more slowly and to have made more time-consuming errors than control boys or girls with diabetes (Holmes, Greer, Dunlap, Tsalikian, & Frentz, 1995). Further, boys appear to lose their gender advantage for perceptual organization skills (Holmes et al., 1992), and those with earlier disease onset and poorer metabolic control have lower performance IQ scores (Schoenle et al., 2002). Boys with diabetes also have been found to have a higher incidence of learning problems and special classroom assistance than controls (Holmes et al., 1992).

Developmental Gains over Time

Prospective studies provide evidence that diabetes relates to learning difficulties. At time of diagnosis, there are no cognitive differences between children with diabetes and control children in the areas of neuropsychological functioning, intellectual potential, and academic achievement (Kovacs, Goldston, & Iyengar, 1992; Northam et al., 1998; Rovet, Ehrlich, & Hoppe, 1988). At one-year follow-up, Rovet et al. (1990) still did not find performance differences, although older children with later disease onset began to evidence a minor decline in verbal functioning, which was significantly lower by 7 years (Rovet & Ehrlich, 1999). Northam et al. (1998, 2001) followed children at comparable intervals, over 2- and 6-year follow-ups, and found that children with earlier disease onset showed smaller verbal gains than controls, although scores remained within the average range. Episodes of severe hypoglycemia significantly predicted lower verbal and full-scale IQ scores at 6-year follow-up.

Kovacs et al. (1992) found that children experienced a decline in both vocabulary scores and school grades 6 years postdiagnosis. Two years later, Kovacs, Ryan, and Obrosky (1994) found lower short-term memory scores consonant with diminished vocabulary, although vocabulary scores remained in the average range. Declines in verbal skills were thought to be mediated by memory dysfunction, although the authors’ single administration of a memory measure precluded testing this hypothesis directly. Unfortunately, gender correlates of learning performance were not evaluated in any of these longitudinal studies.

The present longitudinal study examined the demographic and disease predictors of memory and learning performance as well as the performance strategies of children with diabetes initially and 4 years later. The Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) utilizes five administrations of a 15-word list to evaluate verbal memory and learning (e.g., see Mungas, 1983). Serial position response patterns are thought to reflect different memory and learning strategies. Recency recall suggests a greater dependence on short-term or immediate memory (Klatzky, 1980) and results in poorer overall learning (Delis, Kramer, Freeland, & Kaplan, 1988). In contrast, primacy and medial items that are recalled are thought to be encoded into long-term memory (Delis et al., 1988) and are related to better long-term learning. Generalizability was enhanced with a cross-regional sample of children. Boys with diabetes were anticipated to experience the greatest verbal difficulty and least developmental gain over time. Disease risk factors also were expected to relate to poorer cognitive performance.

Method

Recruitment

Initially, children with IDDM were identified for possible study participation by their upcoming outpatient diabetes appointments. Letters were mailed explaining the study. A follow-up phone call was made to answer questions and to schedule those interested for assessment, usually on the day of their medical appointment. The refusal rate was approximately 9%, with lack of interest, lack of time, or child-care difficulties noted as the most frequent reasons. Children were recruited consecutively from one of two sites. The first site was a university-affiliated Midwestern tertiary level hospital which also provides routine diabetes care for children from around the relatively rural state (Holmes et al., 1992). The second site, in the South, was comprised of four metropolitan hospitals (two university-affiliated tertiary care hospitals and two secondary care hospitals) which all also provide routine care to children with diabetes (Holmes, Greer, Dunlap, et al., 1995). Children received primary medical care, e.g., for inoculations, from their general pediatricians, and their diabetes management from a hospital-based pediatric endocrinologist. Based on routine medical examinations, all children had to be free of secondary disease complications (e.g., retinopathy, neuropathy) and any other major medical or psychiatric conditions, as a means of assuring some parity in patient medical status regardless of recruitment site. For study inclusion, children also had to be between the ages of 7 and 16 and be at least 6 months postdiagnosis, to rule out residual insulin production during the honeymoon period (Johnson, 1995). Children with diabetes were tested either after breakfast or lunch and were asked to bring snacks from home to consume as usual/necessary during the assessment to avoid hypoglycemia.
All children in the Midwestern sample were white, reflecting the low minority composition of that state (Iowa; 3%). In addition, the Midwestern participants were middle-class on average, based on the Hollingshead (1975) four-factor index of occupational and educational status (M SES = 41.5, SD = 10.8). The southern sample also was middle-class on average (M SES = 42.8, SD = 15.0), but was 18% African American.

Subjects were contacted for reevaluation an average of 4.3 years after their initial assessment. Of the initial diabetes sample sought for follow-up evaluation (N = 173), a subsample of 143 participants was enrolled, for a retention rate of 83%. The retention rates were: boys with diabetes (83%), control boys (86%), girls with diabetes (82%), and control girls (72%). The retention rate for control girls was somewhat lower than other groups, but not significantly so, χ²(3) = 1.37, p = .712. The follow-up groups of children were representative of the original study groups on the demographic variables.

Of the 143 diabetes subjects with 4-year follow-up data, 98 had completed the RAVLT at initial and follow-up assessments. Of these, 3 (30.6%) children with diabetes had initial RAVLT scores ≥ 90% and were removed to avoid ceiling effects.

Initially, after a child with diabetes was enrolled in the study, a control child with no chronic health conditions or history of head trauma was recruited from the rosters of participating schools that encompassed a diverse SES range within either the corresponding Midwestern or southern site. Within each grade level, the names of children were selected with the aid of a random numbers table until a suitable match was found for a target child on the variables of grade, gender, race, and SES. Control children were tested at their school, usually during a free period or after school. Examiners were not blinded to the initial versus follow-up status of the assessments. At time of follow-up, control children and their families were contacted via telephone for further study participation (n = 101). Because of ceiling effects on the RAVLT, the data of one child was removed, reducing the control sample to 100 children.

The appropriate institutional review boards approved the study at each hospital and school district involved. Informed written consent and assent was obtained from parents and children, respectively, at each evaluation. Participants received $20 and $30 for initial and follow-up participation, respectively.

**Participants**

At initial assessment, children with diabetes were 11.5 years on average (range, 7–16), with an average age of disease onset of 7.9 years and average disease duration of 3.6 years. Control participants were 12.1 years on average (range, 7–16). At follow-up, participants with diabetes were 15.9 years on average (range, 11–21), with an average disease duration of 8.1 years. Controls had an average age of 16.2 years (range, 11–21).

Analyses of variance (ANOVARs) indicated no differences between the diabetes and control boys and girls on the demographic variables at initial or follow-up testing. Neither boys nor girls with diabetes differed on any of the disease variables (see Table I for group means).

**Assessment**

The RAVLT (Rey, 1964) was administered as part of a larger study. The RAVLT was used to assess children’s ability to remember and learn new verbal information with different, but parallel, versions of word lists composed of 15 concrete nouns (Lezak, 1995). One word list was administered initially and the other at follow-up testing. The percentage of words learned was calculated for each child for each trial.

**Glycosylated Hemoglobin.** A glycosylated hemoglobin (HbA₁) assay, which assesses metabolic control over the previous 6 to 8 weeks (Goldstein, 1984), was conducted on a sample of blood drawn at the time of children’s medical appointments to provide an index of metabolic control at the time of testing. An average HbA₁ value also was calculated based on a mean of 6.5 prior values, obtained before the time of testing, to provide an index of chronic metabolic control. The average HbA₁ measure provides an index of the chronic metabolic milieu of the brain during this period of rapid growth and development. HbA₁ levels were calibrated across hospitals (Holmes, Yu, & Frentz, 1999).

**Hypoglycemic Episodes.** Average number of severe hypoglycemic episodes, defined as episodes of seizures or unconsciousness, was recorded based on retrospective reports of parents and corroborated by medical chart review when possible. Episodes of severe hypoglycemia versus uncomplicated hypoglycemia events were recorded because seizures and unconsciousness are observable events and are more likely to be accurately detected and reported.

**Results**

**Overview of the Analyses**

ANOVARs evaluated memory and learning performance over time on the RAVLT for groups of children to test the hypothesis of greater cognitive vulnerability in boys with diabetes. Next, to explain significant differences in memory or learning, performance strategies, as measured by serial position effects, were evaluated with ANOVAs. Hier-
Archival multiple regression also was used to assess high-risk disease variables as predictors of memory and learning performance.

Developmental Trends in Memory

A repeated measures ANOVA with one within-group factor (time) and two between-group factors (diabetes status and gender) was performed on the percentage of words recalled on Trial 1, an assessment of memory. There was a significant main effect of time, \( F(1, 192) = 19.51, p < .001 \); the percentage of words recalled increased over time. There were no significant interactions.

Developmental Trends in Learning

A repeated measures ANOVA with one within-group factor (time) and two between-group factors (diabetes status and gender) was performed on the average percentage of words learned on Trials 2 through 5, as an assessment of learning. Again, there was a significant main effect of time, \( F(1, 192) = 27.76, p = .0001 \); the average percentage of words learned increased over time. There was also a significant three-way interaction of Time \( \times \) Disease Status \( \times \) Gender, \( F(1, 192) = 7.57, p = .0065 \). Post hoc SNK tests indicated that control girls had significantly higher learning scores initially than all other groups \( (p < .05) \). At follow-up, control girls, who performed equally to control boys and to girls with diabetes, still had significantly higher learning scores than boys with diabetes \( (p < .05) \) (see Figure 1).

Serial Position Effects

Three repeated measures ANOVAs, each with one within-group factor (time) and two between-group factors (diabetes status and gender), were performed on the average percentage of words learned on Trials 2 through 5 from the primacy position of the word lists (Words 1 through 5), the medial position (Words 6 through 10), and the recency position (Words 11 through 15).

Primacy Learning. For words learned in the primacy position, there was a significant main effect of time, \( F(1, 192) = 6.60, p = .0109 \), and a significant three-way interaction of Time \( \times \) Disease Status \( \times \) Gender, \( F(1, 192) = 7.57, p = .0065 \). Post hoc SNK tests indicated that control girls initially learned more words in the primacy position than all other groups \( (p < .05) \). At follow-up, control girls continued to perform significantly better than boys with diabetes only, a performance pattern that mirrored the overall learning results. Paired \( t \) tests revealed that primacy learning increased significantly \( (p < .05) \) over time for both control boys and girls with diabetes and, at follow-up, caught up to the performance of con-

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Table I. Demographic and Disease Characteristics (Means and Standard Deviations) for Groups of Children with Scores on the Rey Auditory Verbal Learning Test at Time of Initial (1) and Follow-up (2) Evaluations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetes</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Girls (N = 38)</td>
<td>Boys (N = 57)</td>
</tr>
<tr>
<td>Age (1) (in years)</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Age (2) (in years)</td>
<td>11.24</td>
<td>2.54</td>
</tr>
<tr>
<td>Grade (1)</td>
<td>5.67</td>
<td>2.74</td>
</tr>
<tr>
<td>Grade (2)</td>
<td>5.38</td>
<td>2.66</td>
</tr>
<tr>
<td>SES</td>
<td>9.27</td>
<td>2.69</td>
</tr>
<tr>
<td>Age of onset (in years)</td>
<td>40.78</td>
<td>14.05</td>
</tr>
<tr>
<td>Disease duration (1) (in years)</td>
<td>7.29</td>
<td>2.90</td>
</tr>
<tr>
<td>Disease duration (2) (in years)</td>
<td>3.9</td>
<td>4.3</td>
</tr>
<tr>
<td>Hypoglycemiaa (1)</td>
<td>8.4</td>
<td>3.19</td>
</tr>
<tr>
<td>Hypoglycemiaa (2)</td>
<td>0.42</td>
<td>0.79</td>
</tr>
<tr>
<td>HbA1 at testing (1)</td>
<td>2.87</td>
<td>1.96</td>
</tr>
<tr>
<td>HbA1 at testing (2)</td>
<td>1.05</td>
<td>0.79</td>
</tr>
<tr>
<td>Average HbA1c (1)</td>
<td>12.74</td>
<td>4.0</td>
</tr>
<tr>
<td>Average HbA1c (2)</td>
<td>11.14</td>
<td>2.83</td>
</tr>
</tbody>
</table>

SES (socioeconomic status) is calculated from Hollingshead (1975). HbA1c = glycosylated hemoglobin.

aHypoglycemia = number of episodes of seizures and unconsciousness.

Average HbA1c is based on a mean of 6.5 HbA1c values (an assessment of metabolic control) prior to (exclusive of) the HbA1c measures obtained at the time of initial and follow-up testing.
control girls, whose scores remained high and did not increase significantly over time \((p = .0654)\). In contrast, the primacy performance of boys with diabetes did not increase, and in fact tended to decrease slightly over time (see Figure 2).

**Medial and Recency Learning.** There was a significant main effect of time for words in both the medial, \(F(1, 192) = 15.33, p = .0001\), and recency positions, \(F(1, 192) = 13.79, p = .0003\), with more words learned at follow-up. There were no significant interactions.

**High-Risk Disease Variables**

In order to assess high-risk disease variables as predictors of memory and learning performance, hierarchical multiple regression analyses were performed on differences in the percentage of words recalled over time. Disease performance predictors included number of severe hypoglycemic episodes involving seizures or loss of consciousness (one subject with 24 hypoglycemic episodes was removed from this analysis), age of disease onset, disease duration, and average HbA1c. Sociodemographic performance predictors included gender and SES.

**Differences in Memory over Time.** The overall model of two demographic and four disease variables was not significant in predicting memory difference scores on Trial 1 over time, \(F(6, 79) = 0.75, p = .6129\).

**Differences in Learning over Time.** Overall, the two demographic and the four disease variables accounted for approximately 19% of variance in predicting diabetes difference scores on Trials 2 through 5, \(F(6, 79) = 2.93, p = .0129\). The two demographic predictors accounted for approximately 6% of the variance, and the four disease variables accounted for approximately 13% of the variance. Gender was the only significant demographic predictor of differences in learning over time \((p = .0315)\), with male gender predicting lower difference scores, i.e., less learning. Disease duration also was a significant predictor of performance \((p = .0086)\), with longer duration predicting less learning over time. However, the Gender \(\times\) Duration product term was not a significant predictor of learning differences over time. Age of disease onset approached significance \((p = .054)\), and with a beta weight of \(-.28\) indicated that children with earlier disease onset tended to have poorer learning scores. See Table II for beta values and variance accounted for by demographic and disease variables.

**Discussion**

The present study provides the first important evidence of gender differences in verbal learning skills over time in children with diabetes, consistent with a male vulnerability hypothesis (Geschwind & Galaburda, 1985; Schoenle et al., 2002). Boys with diabetes failed to make developmental gains on a verbal learning task 4 and a half years later at follow-up, unlike other study groups who made developmental improvements in volume of material learned between the ages of 11 and 15 years (see Figure 1). Strikingly, this developmental plateau occurred for boys with diabetes during midadolescence, which is a period of rapid growth and maturation, when volume and speed of acquisition of new material should increase substantially (Gitomer & Pellegrino, 1985).

The boys’ failure to make significant gains in verbal learning may be related to difficulty with long-term recall of information learned in midadolescence. Specifically, when serial order learning strategies were examined, boys with diabetes showed a plateau in learning words
from the primacy or beginning portion of the word list. The primacy learning of girls with diabetes and control boys increased in volume over 4 years, and the scores of control girls remained high. Only the boys with diabetes demonstrated a primacy plateau, similar to their overall learning plateau. Difficulty with transfer of verbal primacy information from short- to long-term storage (Delis et al., 1988) may explain the learning plateau seen in this study. Such difficulty also may explain decreasing vocabulary scores over 8 years (Kovacs et al., 1994) and declining cued learning over a 6-year period (Northam et al., 2001) found in other studies, suggesting a reduction in expected developmental gains in verbal acquisition of information.

The relative male disadvantage for verbal learning in the general child population (Kaufman & Doppelt, 1976; Delis et al., 1987; Kramer et al., 1997) was mirrored in the present study with the trend of control boys to obtain lower scores than control girls (see Figure 1). Further, control girls had better scores than boys with diabetes both initially and at follow-up, and boys with diabetes failed to increase their learning scores over time. The mechanism of the poorer rote verbal learning of boys with diabetes on the RAVLT is unknown but may be associated with asymmetrical hemispheric cerebral blood flow for boys during hypoglycemia, with lower left- than right-brain hemisphere perfusion (Jarjour, Ryan, & Becker, 1995). Repeated, even relatively mild, asymptomatic hypoglycemia has been found to have long-term detrimental effects on cognitive skills in children (Golden et al., 1989). One might anticipate a cumulative adverse effect to left-hemisphere dominant verbal skills in boys with repeated exposure to hypoglycemia over time, underscoring the need to reduce hypoglycemia in children and adolescents (Northam et al., 1998, 2001; Rovet & Ehrlich, 1999). Men have been shown to experience hypoglycemia at higher blood glucose levels than women, and correspondingly to have greater cognitive disruption than women while hypoglycemic (Gonder-Frederick, Cox, Driesen, Ryan, & Clarke, 1994; Draelos et al., 1995). Should this prove to be the case for boys, it will be important to avoid even mild hypoglycemia, particularly during school. However, should this be the purported mechanism, the effect of hypoglycemia would have to be mild and chronic because number of severe hypoglycemic episodes was not a significant predictor of poorer memory or learning in the present study. Alternatively, there may be measurement error with the retrospective parent report of observable hypoglycemic seizures and unconsciousness over a relatively long interval that may have obscured obtaining an association in the present study.

Gender differences in verbal learning also were reflected in the regression results, as gender was the only significant demographic predictor of diabetes differences in learning over time (standardized \( \beta = -0.23, p < 0.05 \)), outweighing the effect of the traditionally influential predictor of SES in this predominantly middle-class sample (standardized \( \beta = -0.14 \)). However, the most potent predictor of RAVLT performance was disease duration (standardized \( \beta = -0.40 \)), with longer disease duration related to poorer learning. Nevertheless, despite the significant learning predictors of gender and disease duration, the Gender \( \times \) Duration interaction term was not a significant performance predictor. These results indicate that the cumulative and chronic exposure to metabolic abnormalities characteristic of diabetes is the major risk factor related to poor learning performance over time and that, independent of disease duration, male gender is another significant vulnerability factor related to poor learning.
Consistent with the significant disease duration predictor of RAVLT scores, some evidence was found that diabetes in general may have a subtle impact on the rote verbal learning skills of girls as well. Despite similar demographic features, girls with diabetes performed significantly less well than control girls on this verbal task initially, with a level of performance that was comparable to that of control boys. Although the group scores were not significantly different at follow-up, the trend remained for control girls to outscore girls with diabetes. These findings provide some preliminary evidence that girls with diabetes may lose their gender advantage with verbal material, much like boys with diabetes appear to lose their gender advantage with spatial information (Holmes et al., 1992; Schoenle et al., 2002). However, it is important to note that even though these differences were statistically significant, they could not be considered clinically significant, because unlike their male counterparts, girls with diabetes showed significant developmental gains in verbal skills over time. If these preliminary differences between groups of girls are replicated, they may suggest that chronic metabolic alteration throughout childhood may exert a subtle, yet detectable, impact on the laboratory learning skills of all children with diabetes (Northam et al., 1998, 2001) that may differ only in magnitude of the effect in association with gender.

In the present study, boys with diabetes did not experience developmental gains in primacy learning or verbal learning over a 4-year follow-up period through midadolescence. Girls with diabetes also tended to score less well than their demographically matched controls. These differences in learning help amplify earlier findings (Northam et al., 2001; Rovet & Ehrlich, 1999) by highlighting demographic and disease risk factors that may place some children at potentially greater risk for educational difficulty. In addition, disrupted learning of primacy information may be the locus of diminished long-term verbal acquisition and should be a focus of additional investigation. It will be important to monitor children's

| Table II. Hierarchical Multiple Regression of Demographic and Disease Predictors of Differences in Percentage of Words Learned over Time |
|-----------------------------|-----------------|-----------------|----------|--------|
| Variables                  | Standardized β | Unstandardized β | Variance | p-value |
| 1. Demographic variables   |                 |                 |          |        |
| Gender*                    | −0.23           | −6.14           | 0.0616   | 0.0315 |
| SES                        | −0.14           | −0.12           | 0.1999   |        |
| 2. Disease variables       |                 |                 | 0.1324   |        |
| Disease duration           | −0.4            | −1.65           | 0.0086   |        |
| Hypoglycemic episodes      | 0.19            | 1.33            | 0.0855   |        |
| Age of onset               | −0.28           | −1.17           | 0.0339   |        |
| Average HbA1               | −0.03           | −0.14           | 0.7768   |        |
| 3. Gender × Duration       | 0.26            | 0.73            | 0.4584   |        |
| Total                      |                 |                 | 0.194    |        |

SES (socioeconomic status) is calculated from Hollingshead (1975). HbA1 = glycylated hemoglobin.

*Female = 0; male = 1.
educational development to help ensure that subtle laboratory learning difficulties do not take a cumulative educational and/or secondary emotional toll (Jacobson et al., 1997; Bryden et al., 2001).

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