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Absence of an association between insulin-dependent diabetes mellitus and developmental learning difficulties

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For several years, investigators have been examining the relationship between learning difficulties and a variety of immunological disorders. Two recent studies by Hansen and colleagues reported a negative association between Type 1 diabetes and reading disabilities (dyslexia): subjects with Type 1 diabetes had a lower prevalence of dyslexia than their nondiabetic relatives. In order to control for the impact of environmental variables on learning, we investigated the relationship between Type 1 diabetes and learning problems in 27 sibling pairs, ranging in age from 6 to 20 years. One child in each pair had Type 1 diabetes, and the other child was the unaffected sibling closest in age. Children were assessed for cognitive skills, academic achievement in reading, mathematics, and written language, as well as for speech articulation and motor coordination. Other variables that were examined included handedness, behavioural variables, medical history, and pregnancy and birth complications. We found no significant differences between the 27 children with Type 1 diabetes and their unaffected siblings on any of the cognitive, academic achievement, or speech articulation measures. There were also no significant differences on handedness, behavioural variables, or health history.

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Both Type 1 (insulin-dependent) diabetes mellitus and dyslexia have been shown to be significantly influenced by genetic factors (FIELD 1988; VOGLER et al. 1984). Previously, there has been little evidence to suggest that the two might be related; however, two recent studies reported that people with Type 1 diabetes have a lower prevalence of dyslexia than their nondiabetic relatives (HANSEN et al. 1986, 1987). The frequency of dyslexia among diabetic subjects was 2.6% (3/114), whereas the frequency of dyslexia among unaffected relatives was 27% (43/157). HANSEN et al. (1986, 1987) suggested that the relationship between Type 1 diabetes and dyslexia may be due to a genetic connection between chromosomes 6 and 15. The HLA complex on chromosome 6 is involved in the susceptibility to Type 1 diabetes (e.g., FIELD et al. 1986; FIELD 1989). SMITH et al. (1983) reported significant lod score evidence for linkage between dyslexia transmitted in an apparent autosomal dominant fashion, and a chromosome 15 centromeric heteromorphism, although subsequent researchers (e.g., BISGAARD et al. 1987) have failed to replicate these findings. Smith and colleagues (SMITH et al. 1989, 1991) also reported evidence suggesting a linkage between the HLA region on chromosome 6 and dyslexia, which is particularly relevant to the possible relationship with Type 1 diabetes. They also suggested the possibility of genetic heterogeneity, since some families with positive chromosome 6 lod scores showed no evidence for chromosome 15 linkage and vice versa.

The studies of Type 1 diabetes and dyslexia by HANSEN et al. (1986, 1987) were compromised by three problems. First, the definition of dyslexia, in terms of assessment tools or cutoff scores, was absent from these articles, so that the prevalence data that they obtained cannot be compared with any other published estimates. Second, families with diabetes were ascertained through probands in a diabetes hospital, who, the investigators reasoned, were most likely to be insulin-dependent. The frequency of "diabetes" which they found in the relatives of these probands was, however, quite high, suggesting that those relatives might have included some individuals with non-insulin-dependent diabetes. Third, no control families were studied, so it is impossible to determine whether the frequency of dyslexia which they obtained with

their diagnostic criteria was decreased in the subjects with diabetes relative to the general population, or increased in the nondiabetic relatives.

An association between dyslexia and Type 1 diabetes could provide important information about the genetic basis of each disorder. For all of these reasons, we explored this topic further, controlling for the impact of environment by studying siblings. Rather than deciding *a priori* to focus on a specific type of learning problem such as dyslexia, we performed a broad assessment of cognitive skills and some motor skills in children with Type 1 diabetes and their unaffected siblings. Based on the reports of HANSEN et al. (1986, 1987), it was hypothesized that the unaffected siblings would show significantly more deficits in cognitive and motor skills than would the children with Type 1 diabetes.

Subjects and methods

To be potential subjects, children with Type 1 diabetes had to have at least one unaffected sibling, and had to have been recently diagnosed with Type 1 diabetes (between 1987 and 1990). Subjects had to have developed Type 1 diabetes after the age of five, because of other reports of cognitive deficits in children whose Type 1 diabetes developed before five years of age (ROVET et al. 1987; RYAN et al. 1985). The Diabetes Clinic at the Alberta Children's Hospital sent out introductory letters to families of children with Type 1 diabetes on the current caseload. This letter gave a brief explanation about the project, and included a form and a self-addressed stamped envelope for the parents to return to the research team if they agreed to receive a telephone call to hear more about the study. In total, 37 parents returned the form. Of those 37 replies, 22 familes eventually agreed to participate in the study, 12 families refused to participate (primarily because of the time required), and three families contained children who were either too young or too old to participate. The response rate was somewhat low; however, the clinic personnel led us to expect a response rate in this range because their patients with Type 1 diabetes have been very intensively studied in the past few years.

Families were also recruited through family physicians in two other cities. From the 11 families who replied to introductory letters, five agreed to participate in the study, three refused, and three families had children who were not appropriate for the study because they had developed Type 1 diabetes before the age of five.

Subjects were 27 sibling pairs, aged 6 to 20 years. One child in each pair had Type 1 diabetes, and the other child was the sibling closest in age to the child with Type 1 diabetes. None of the siblings of the diabetic children had Type 1 diabetes. There were 16 females and 11 males with Type 1 diabetes (mean age = 12.44 years, SD = 3.01), and 10 female siblings and 17 male siblings (mean age = 12.12 years, SD = 3.71). It was not possible to match children with Type 1 diabetes to their unaffected siblings on the basis of sex because of the fact that the majority of families either had only two children, or had only one other child between the ages of 6 and 20 years.

All participants and/or their parents provided written confirmation of their voluntary consent. The study was approved by the Conjoint Medical Ethics Committee of the University of Calgary, and by the Alberta Children's Hospital Research Committee.

Psychoeducational and motor assessment. — Children were assessed using the Wechsler Intelligence Scale for Children Revised (WISC-R; WECHSLER 1974), the reading, mathematics, and written language achievement subtests from the Woodcock Johnson Psychoeducational Battery (WOODCOCK and JOHNSON 1977), the bilateral coordination subtest from the Bruininks Oseretsky Test of Motor Proficiency (BOTMP; BRUININKS 1978), and the WEISS Comprehensive Articulation Test (WCAT; WEISS 1980), as listed in Table 1. Two subjects who were over the age of 17 were given the Wechsler Adult Intelligence Scale-Revised (WAIS-R; WECHSLER 1981). The bilateral coordination subtest of the BOTMP was used in the assessment because problems in this area have been found to co-exist with dyslexia (REGEHR and KAPLAN 1988). The WCAT was used because of some pilot data we had collected which suggested that unaffected siblings of children with Type 1 diabetes had more speech problems than did the children with Type 1 diabetes.

Parent's questionnaire. — One parent of each child completed a questionnaire on the child's personal history and any familial history of learning difficulties (e.g., hyperactivity, reading problems), immune disorders (e.g., allergies, asthma) and autoimmune disorders (e.g., rheumatoid arthritis). The Medical History Questionnaire and scoring protocol from BURKE et al. (1988) were adapted

Table 1. Means and standard deviations

Variable	Diabetic group (n = 27)		Sibling group (n = 27)	
	Mean	(SD)	Mean	(SD)
WISC-R/WAIS-R				
Full scale IQ	109.15	(13.85)	110.00	(9.78)
Verbal IQ	106.19	(15.50)	107.04	(9.65)
Information	10.93	(2.72)	11.43	(1.77)
Similarities	11.22	(3.41)	11.11	(3.01)
Arithmetic	11.22	(3.12)	11.25	(3.03)
Vocabulary	10.33	(2.86)	10.50	(2.06)
Comprehension	10.96	(3.25)	11.82	(2.16)
Digit span	10.07	(2.67)	10.30	(2.73)
Performance IQ	110.48	(13.77)	111.18	(11.05)
Picture completion	10.78	(2.78)	10.21	(2.13)
Picture arrangement	11.93	(2.37)	11.82	(2.16)
Block design	11.89	(3.12)	11.86	(2.62)
Object assembly	11.52	(2.77)	12.50	(2.50)
Coding	11.30	(2.96)	11.89	(2.78)
Mazes	14.00	(2.43)	13.19	(2.98)
Woodcock Johnson psychoeducational battery				
Percentile rank for age:				
*Reading achievement	58.07	(22.48)	60.11	(22.17)
Math achievement	60.81	(30.64)	62.48	(23.59)
*Written language achievement	61.35	(27.92)	63.33	(27.93)
Weiss articulation	97.97	(2.52)	97.73	(3.11)
Bruininks Oseretsky test of motor proficiency				
Bilateral coordination (standard score)	16.95	(5.04)	18.48	(4.78)

* Significant sex difference at $p < 0.05$

for this section of the questionnaire. For each item, 1 point was awarded if the child was afflicted, 0.50 points for each member of the child's immediate family afflicted (parents and/or siblings), and 0.25 points for each second degree relative afflicted (aunts, uncles, cousins, and/or grandparents). Only blood relatives of the child were included.

Handedness scores for the child, the mother, and the father were determined by an abbreviated version of CROVITZ and ZENER's scale (1962) that featured five items: printing, throwing a ball, drawing a picture, holding scissors, and unscrewing the lid of a jar. For each item, zero points were awarded for a response of "always right", 1 point for "usually right", 2 points for "either hand", 3 points for "usually left," and 4 points for "always left." Thus, the overall handedness score could range from zero points indicating strong right-handedness to 20 points indicating strong non-righthandedness. Questions dealing with the handedness of other family members were also included.

Following BURKE et al. (1988), 0.50 points was awarded for each parent and/or sibling who was nonrighthanded, 0.25 points for each blood relative of the child who was nonrighthanded. One point was awarded if the child was reported to exhibit any degree of nonrighthandedness, which was broadly defined as any score greater than zero on the handedness scale. An overall index of familial nonrighthandedness was generated by adding together the points awarded for nonrighthandedness in the child, parents, siblings, and blood relatives.

The 10-item Abbreviated Symptom Questionnaire (ASQ; CONNERS 1973) was also included in the questionnaire, as an indicator of children who might have some of the characteristics of Attention Deficit Hyperactivity Disorder (ADHD). The ASQ has been established to be a valid and reliable measure for identifying ADHD (CONNERS 1973; ROSENBERG et al. 1989), although reliance on it for the diagnosis of ADHD has been criticized by many (e.g., ULLMAN et al. 1985), particularly with respect to the way researchers have used cutoff scores to define hyperactive samples. Thus, we made no further attempt to establish a clinical diagnosis (e.g., via the use of cutoff scores), but instead, we used the ASQ to identify parental concerns associated with ADHD.

The final section of the questionnaire asked about pregnancy and birth complications (e.g., toxemia, Caesarian section, cyanosis, jaundice)

(LEVINE 1980). One point was awarded for each item that was answered "true", and overall indices for both pregnancy and birth complications were calculated by adding together the responses for each individual complication. The difference between the child's date of birth and the due date was used to calculate the number of days the birth was premature or postmature. The mother was also asked how much weight she had gained while pregnant, how many pregnancies she had, and what birth order the child was.

Statistical analyses

Data were collected and analyzed using the computer program SPSS-PC+. A series of MANOVAs were used to compare children with Type 1 diabetes and their unaffected siblings on the psychoeducational assessment measures. Parental report data on the prevalences of learning difficulties, immunologic dysfunction, and pregnancy and birth complications were analyzed using chi-square tests of independence for individual variables, and a MANOVA for the overall indices.

Results

Psychoeducational assessment

A series of MANOVAs were conducted comparing the children with Type 1 diabetes to their unaffected siblings. For each MANOVA, the overall effects for group, sex, and the group × sex interaction were examined.

Children with Type 1 diabetes did not differ significantly from their unaffected siblings in terms of full scale IQ, verbal IQ, performance IQ, or in terms of their scaled score on any of the individual subjects that contribute to those IQ scores ($p > 0.05$). Because the WISC-R and WAIS-R both yield standardized fullscale, verbal, and performance IQ scores, no attempt was made to adjust the scores of the two subjects who were given the WAIS-R.

No significant group differences emerged for the reading skills, mathematics skills, or written language skills evaluated on the Woodcock-Johnson Psychoeducational Battery ($p > 0.05$); however, there was a significant sex difference (Wilk's lambda $F(3, 47) = 6.19$, $p < 0.01$). Girls performed significantly better in reading skills ($F(1, 49) = 4.93$, $p < 0.05$), and in written language skills ($F(1, 49) = 11.86$, $p < 0.01$).

Scores on the Woodcock Johnson Psychoeducational Battery were also examined to determine whether any met the conventional definition of learning difficulties. Using a two-year delay as our criterion, we calculated 162 discrepancy scores, based on chronological age at testing and age-equivalent scores (reading, mathematics, and written language for each of the 54 children). Only five children were found to have *at least* a two-year delay in one or more of the areas examined. Four of the five children had Type 1 diabetes, and of those four, two were significantly delayed in written language, one was delayed in both written language and reading, and one was delayed only in reading. One of the siblings had a two-year delay in mathematics skills. The two groups were not significantly different in terms of their discrepancy scores ($p > 0.05$); however, the overall effect for sex approached significance (Wilk's lambda $F(3, 47) = 6.07$, $p < 0.10$). Girls performed significantly better and had significantly higher discrepancy scores on written language skills ($F(1, 49) = 6.07$, $p < 0.05$).

There were also no significant group differences on the measure of speech articulation ($p > 0.05$), and on the measure of bilateral coordination ($p > 0.05$)

Parent's questionnaire

Chi-square tests of independence were used to compare the children with Type 1 diabetes and their siblings in terms of various learning difficulties and immunologic diseases. The children with Type 1 diabetes were not significantly different ($p > 0.05$) from their siblings in the prevalence of learning or attention problems. Similarly, no significant group differences emerged in the prevalence of nonrighthandedness or immunologic disorders ($p > 0.05$).

A MANOVA was conducted using the overall indices of pregnancy and birth complications, the mother's weight gain, the child's birth weight, and the number of days premature/postmature as the dependent variables. No significant differences emerged ($p > 0.05$). A number of chi-square tests of independence were conducted comparing the children with Type 1 diabetes and their siblings in terms of the individual pregnancy and birth complications. No significant differences emerged ($p > 0.05$).

Discussion

HANSEN et al. (1986, 1987) suggested that Type 1 diabetes and dyslexia could be due to the same dominantly inherited genetic susceptibility, and that an environmental factor possibly acting in utero could elicit dyslexia, which in turn would protect against later development of Type 1 diabetes. If this were the case, it would be expected that the unaffected siblings of children with Type 1 diabetes would show significant deficits in cognitive skills related to language. The results of the present study showed that, contrary to the initial hypothesis, there were no differences between the unaffected siblings and the children with Type 1 diabetes on any of the cognitive skills that were assessed.

One concern is whether our sample size afforded us significant power to detect the differences reported by Hansen and colleagues. They found a 27 % rate of dyslexia in family members: a comparable rate in our sample would have revealed a minimum of seven siblings affected by dyslexia, indicating our sample size was sufficient. In reality, we found no siblings with significant reading deficits. When we used a two-year delay as a criterion for learning problems, five of the 54 children had at least a two-year delay in reading, mathematics, and/or written language. Four of those five children had Type 1 diabetes, which is contrary to the initial hypothesis. This 10 % prevalence of school problems was approximately what would be expected in any population sample. Thus, the results of the present study have failed to replicate the findings of HANSEN et al. (1986, 1987). Even though we used a broad assessment of cognitive skills, and even though we used unaffected siblings as controls, no significant group differences emerged.

HANSEN et al. (1986, 1987) also argued that the relationship between Type 1 diabetes and dyslexia is in fact a case of pleiotropism, which occurs when certain genetic predispositions manifest themselves in diverse ways in different members of the same family (BORECKI et al. 1985). The fact that we found no relationship between Type 1 diabetes and dyslexia may indicate that Type 1 diabetes and learning difficulties like dyslexia may be related within members of the extended family (as studied by Hansen et al.), and not necessarily within siblings. Further investigations with larger sample sizes are needed to explore the relationships between immunologic dysfunction and learning difficulties in greater detail.

In summary, in spite of our relatively small sample size, our investigation of this topic was better controlled than those of Hansen et al. Our sample was sufficient to confirm other known characteristics of cognitive skills: we found the expected female superiority for language skills, and we found that approximately 10 % of the sample had a two-year delay in reading, written language, or mathematics. The fact that we found no support for a relationship between any language skills and Type 1 diabetes with subjects matched for environment (sibling pairs) and assessed with standardized tests of cognitive skills, suggests that the relationship is nonexistent or very weak at best.

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