Type 1 Diabetes in Parents and Risk of Attention Deficit/Hyperactivity Disorder in Offspring: A Population-Based Study in Sweden

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OBJECTIVE

To explore whether a family history of type 1 diabetes (T1D) is associated with an increased incidence of attention deficit/hyperactivity disorder (ADHD) in offspring.

RESEARCH DESIGN AND METHODS

Individuals with T1D were identified from the nationwide Swedish National Hospital Discharge Register and Swedish Outpatient Register in Sweden and were linked to the Swedish Multi-Generation Register to identify their offspring. Cox regression was used to calculate the hazard ratio (HR) of ADHD in offspring of patients with T1D compared with the general population.

RESULTS

A total of 15,615 individuals were born after their parents were diagnosed with T1D. After a set of confounding factors was controlled for, offspring of T1D patients had a significantly increased risk of ADHD with an HR of 1.29 (95% CI 1.15–1.42). Maternal T1D was associated with an enhanced risk of ADHD (HR 1.35 [95% CI 1.18–1.55]) compared with paternal T1D (HR 1.20 [95% CI 1.03–1.41]), but the difference was not statistically significant.

CONCLUSIONS

In this retrospective cohort study, we found that a parental history of T1D was associated with a 29% increased risk of being diagnosed with ADHD. However, the underlying mechanisms need to be explored in future studies.

The incidence of type 1 diabetes (T1D) has been increasing globally during recent decades. In the U.S., T1D incidence has been rising by as much as 5.3% annually (1). In Europe, an annual 3% increase in the incidence of T1D has been reported (2). The incidence of T1D is predicted to rise by an estimated 70% between 2005 and 2020 (2). A similar temporal trend has been noted in Sweden (3,4). The etiology of T1D remains largely unknown, but it is widely accepted that T1D is one disease caused by multiple genetic and environmental factors. Individuals with T1D need lifelong insulin therapy, and they have a shorter life expectancy (5,6). T1D can cause long-term dysfunction, damage, and even failure of many organs. Previous studies have found that children with T1D have poorer academic achievement, memory, motor speed, visual spatial ability, and hand-eye coordination (7–9). In addition, chronic hyperglycemia might increase neuronal vulnerability (10,11) and delay myelination of the developing brain (12), which suggests that individuals with T1D may experience central nervous system damage.

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Attention deficit/hyperactivity disorder (ADHD) is a mental disorder and mostly affects children and adolescents (13,14). Its etiology is complex and can be influenced by the interaction of multiple genetic and environmental factors (15), including viral infection, maternal smoking and alcohol drinking during pregnancy, low birth weight, and lead contamination (16). Available evidence suggests that women with T1D have impaired oocyte quality and reduced fertility (17,18). T1D can also damage sperm quality, DNA integrity, and the ingredients of seminal plasma (19). Fetal brain development might be delayed in a hyperglycemic intrauterine environment, with potential long-term implications for cognitive function (20). A lower cognitive function was found among adolescent offspring of women with T1D compared with the general population (20). A recent study found that epigenetic mechanisms related to specific neurodevelopmental processes, such as neural tube development and peroxisomal mechanisms, are associated with ADHD (21). Based on the evidence above, we hypothesized that offspring of T1D patients might experience increased risk of ADHD compared with the general population. We further examined whether the risk of ADHD in offspring was different and dependent on whether the diagnosis of T1D was on either the maternal or paternal side.

RESEARCH DESIGN AND METHODS

Study Population

This retrospective cohort study was approved by the ethics committee at Lund University, Sweden. We used the Swedish National Hospital Discharge Register and the Swedish Outpatient Register to identify patients diagnosed with T1D between 1970 and 2012. The Swedish National Hospital Discharge Register was founded by the National Board of Health and Welfare. The quality of the Swedish National Hospital Discharge Register is generally reliable; a recent review suggested general positive predictive value of ~90% (22). The Swedish Outpatient Register was founded in 2001 and has complete coverage. T1D patients were retrieved from these registries according to the ICD-8 (1970–1986, code 250), ICD-9 (1987–1996, code 250), and ICD-10 (1997-, ICD code E10) code. Only those with a diagnosis age of <20 years were defined as patients with T1D to exclude the possibility of including patients with type 2 diabetes. We further linked with the Swedish Multi-Generation Register to identify the offspring who were born after parental diagnosis of T1D. The Swedish Multi-Generation Register contains data on the biological parents of index persons born in or since 1932 and registered in Sweden since 1961. The Multi-Generation Register contains data on >3.2 million families and >12 million individuals. A total of 15,615 offspring were born after parental diagnosis of T1D. Up to 100 persons from the general population, without a diagnosis of T1D in parents, were matched to the study cohort according to sex and date of birth. Additional linkages were made to Statistics Sweden's Total Population Register and to the Population Housing Census to obtain information on individual-level characteristics such as years of education, to the Cause of Death Register to identify date of death, and to the Emigration Registry to identify date of emigration. All linkages were performed using individual national identification numbers, which were replaced with serial numbers in order to preserve anonymity.

Study Outcome

Individuals with ADHD were identified from the Swedish National Hospital Discharge Register and the Swedish Outpatient Register. Individuals with ADHD were identified according to ICD-9 code 314 and ICD-10 code F90. Only primary diagnoses of ADHD were assessed in this study. Individuals with other neurodevelopmental disorders, such as mental retardation (ICD-9 codes 317–319 and ICD-10 code F70–F79), autism spectrum disorders (ICD-9 code 299B and ICD-10 code F840), and Tourette syndrome (ICD-9 code 307C and ICD-10 code F952), might have comorbidities of ADHD; thus, patients with ADHD with a secondary diagnosis of these neurodevelopmental disorders were excluded in this study.

Adjustment Variables

Other variables that may be associated with ADHD were adjusted for in the analyses. The following were used as adjustment variables: year of birth of the offspring (modeled as a continuous variable to account for follow-up time and attained age as well as incidence trend of ADHD), sex of the offspring (male or female), maternal history of ADHD (yes or no [identified from diagnoses in the Swedish Hospital Discharge Registry and the Swedish Outpatient Registry using the same diagnostic codes as noted above]), paternal history of ADHD (yes or no [diagnoses being the same as that for maternal history]), highest educational level on the maternal and paternal side during the study period (<9, 9–11, or ≥12 years), maternal and paternal age at birth (<25, 25–34, or 35+ years), parental disposable income (lowest, middle-low, middle-high, or highest), maternal urinary tract infection during pregnancy (yes or no), maternal smoking during pregnancy (yes or no), small for gestational age (yes or no), low Apgar score (yes or no), hypoglycemia (yes or no), and other psychiatric disorders on the maternal and/or paternal side (yes or no). Low Apgar score was defined as an Apgar score of 0–3 at 1 and 5 min. Low Apgar score might be caused by many factors, but the vast majority of cases of Apgar scores between 0 and 3 at 5 min are due to perinatal asphyxia.

Statistical Analysis

Cox regression was used to calculate hazard ratios (HRs) for ADHD in offspring of T1D patients compared with control subjects. We calculated person-years at risk for our cohort from date of birth to the earliest of the date of diagnosis of ADHD, death, emigration, or the end of the study period (31 December 2012)—whichever came first. We censored individuals at the time of death, at the end of the follow-up period, or at the time of emigration. The proportional hazards assumption was tested using cumulative martingale residuals. All analyses were performed using SAS, version 9.2.

Sensitivity Analysis

We did a sensitivity analysis to exclude the possibility of chance findings. We excluded cases of ADHD that were identified from the Swedish Outpatient Register to exclude the possibility of detection bias.

RESULTS

A total of 15,615 individuals were born after parental diagnosis of T1D, and 1,380,829 children with parents without a diagnosis of T1D were matched control subjects (Table 1). After a median of 25 years and accumulated 389,154 person-years of follow-up, 367 (2.4%) of those with parental T1D diagnosis were

Table 1—Baseline characteristics in offspring of parents with T1D and matched control subjects

	Study cohorts		Matched control subjects	
	No. of individuals	%	No. of individuals	%
Overall	15,615	100.0	1,380,829	100.0
Offspring's sex				
Female	7,608	48.7	670,520	48.6
Male	8,007	51.3	710,309	51.4
Paternal age at birth, years				
<25	2,117	13.6	155,619	11.3
25–34	9,965	63.8	933,622	67.6
35+	3,533	22.6	291,588	21.1
Maternal age at birth, years				
<25	3,929	25.2	318,911	23.1
25–34	9,850	63.1	919,548	66.6
35+	1,836	11.8	142,370	10.3
Paternal ADHD				
No	15,458	99.0	1,372,616	99.4
Yes	157	1.0	8,213	0.6
Maternal ADHD				
No	15,483	99.2	1,372,989	99.4
Yes	132	0.8	7,840	0.6
Other paternal psychiatric disorders				
No	13,517	86.6	1,254,268	90.8
Yes	2,098	13.4	126,561	9.2
Other maternal psychiatric disorders				
No	12,794	81.9	1,211,691	87.8
Yes	2,821	18.1	169,138	12.2
Paternal education, years				
1–9	2,032	13.0	183,485	13.3
10–11	8,599	55.1	670,157	48.5
12+	4,939	31.6	500,732	36.3
Unknown	45	0.3	26,455	1.9
Maternal education, years				
1–9	1,557	10.0	133,794	9.7
10–11	7,541	48.3	604,936	43.8
12+	6,473	41.5	613,165	44.4
Unknown	44	0.3	28,934	2.1
Parental income				
Lowest	3,267	20.9	333,262	24.1
Middle-low	4,038	25.9	335,539	24.3
Middle-high	4,111	26.3	336,015	24.3
Highest	4,066	26.0	336,012	24.3
Unknown	135	0.9	40,001	2.9
Urinary tract infection during pregnancy				
No	13,761	88.1	1,245,445	90.2
Yes	1,854	11.9	135,384	9.8
Maternal smoking during pregnancy				
No	11,254	72.1	988,801	71.6
Yes	2,219	14.2	151,868	11.0
Unknown	2,142	13.7	240,160	17.4
Small for gestational age				
No	15,295	98.0	1,352,194	97.9
Yes	320	2.0	28,635	2.1
Low Apgar score				
No	15,178	97.2	1,364,942	98.8
Yes	437	2.8	15,887	1.2
Hypoglycemia				
No	14,266	91.4	1,362,922	98.7
Yes	1,349	8.6	17,907	1.3

diagnosed with ADHD, whereas only 1.5% of the matched control subjects were diagnosed with ADHD. The incidence of ADHD was higher in men compared with women and was higher for those with a family history of ADHD and other psychiatric disorders and for those small for gestational age and with maternal smoking during pregnancy. In addition, lower education level was associated with an increased incidence of ADHD.

We further calculated the HR of ADHD in offspring of parents with T1D compared with matched control subjects (Table 2). We did a sequential covariate adjustment by using Cox regression and started with an unconditional model (crude model) and then computed four additional models with sequential adjustments. The crude model showed an increased HR of 1.57 (95% CI 1.42–1.74). The incidence of ADHD (HR 1.29 [95% CI 1.15–1.42]) was still significantly higher after all the confounding factors listed in Table 1 were controlled for.

We further stratified the analyses by paternal and maternal T1D and parental income (Table 3). Maternal T1D (HR 1.35 [95% CI 1.18–1.55]) was associated with a higher risk of ADHD in the offspring compared with paternal T1D (HR 1.20 [95% CI 1.03–1.41]), but no statistically significant difference between parental sex was noted. For offspring whose parents had the highest disposable income, the risk of ADHD was similar to that of matched control subjects. However, offspring whose parents had relatively lower income showed a significantly increased incidence of ADHD.

Table 2—Association between T1D in parents and ADHD in offspring

Sequential models	HR	95% CI	*P*
Model 1	1.57	1.42–1.74	<0.0001
Model 2	1.57	1.42–1.75	<0.0001
Model 3	1.53	1.38–1.69	<0.0001
Model 4	1.42	1.28–1.58	<0.0001
Model 5	1.29	1.15–1.42	<0.0001

Model 1, crude; model 2, adjusted for year at birth and sex; model 3, adjusted for year at birth, sex, and parental history; model 4, adjusted for year at birth, sex, and parental history of ADHD and other psychiatric disorders; model 5, adjusted for year at birth, sex, parental history of ADHD and other psychiatric disorders, parental education and income, small for gestational age, maternal smoking and urinary tract infection during pregnancy, low Apgar score, and hypoglycemia.

Table 3—Adjusted HR of ADHD in offspring stratified by parental T1D and parental income

	HR	95% CI	*P*
Parental T1D status			
No parental history	Ref.		
Paternal T1D	1.20	1.03–1.41	0.02
Maternal T1D	1.35	1.18–1.55	<0.0001
Parental income			
No parental history	Ref.		
Lowest	1.39	1.14–1.70	0.00
Middle-low	1.27	1.04–1.55	0.02
Middle-high	1.59	1.31–1.91	<0.0001
Highest	1.07	0.84–1.37	0.57

HR was adjusted for year at birth, sex, parental history of ADHD and other psychiatric disorders, parental education and income, small for gestational age, maternal smoking and urinary tract infection during pregnancy, low Apgar score, and hypoglycemia.

Sensitivity Analyses

After exclusion of cases of ADHD identified from the Hospital Outpatient Register, the observed association was still significant (Supplementary Table 1).

CONCLUSIONS

In this retrospective cohort study, we identified a total of 15,615 individuals who were born after their parents were diagnosed with T1D. This is, to our best knowledge, the first nationwide study to explore the incidence of ADHD in offspring of patients with T1D. We found that the risk of ADHD was 1.29 times higher among offspring with a parental T1D diagnosis compared with the general population. Several potential mechanisms might explain the current findings. Firstly, patients with T1D might have limited ability to work, especially for those with complications. One study in Sweden found that patients with T1D with complications were less likely to be employed (23). Similar data were reported in the U.K., i.e., that it was hard for patients with T1D to obtain employment and they had to change jobs because of their condition (24). Besides employment ability, another Swedish study suggested that patients with diabetes had a lower disposable income and a higher disability pension than healthy individuals (25). It is known that lower parental education, single-parent families, and welfare benefits are all associated with an increased incidence of ADHD in offspring (26,27). It is thus possible that offspring of patients with T1D might live in a relatively deprived environment and have a consequently increased risk of ADHD. However, the increased incidence of ADHD in offspring of T1D patients was still significant even when we adjusted for parental disposable income and education levels, which suggests that other mechanisms might be related to the current findings. Secondly, previous studies have suggested that patients with T1D have impaired DNA integrity in the germ cells (28). In addition, epigenetic modifications during spermatogenesis or oogenesis might also be damaged (19), which might be associated with ADHD.

An important strength of this study is that it is a nationwide study and the number of individuals with a parental diagnosis of T1D is large enough so that we have sufficient study power to look at associations. All data were retrieved from Swedish registers that are of high quality and have national coverage. The prospective study design and the completeness of the follow-up of patients are other major advantages of the current study.

One limitation of this study is that cases of ADHD were not validated in the Swedish National Hospital Discharge Register and the Swedish Outpatient Register, although the quality of these registers is generally reliable (22). In addition, some individual-level risk factors such as lead contamination and viral infection were lacking in our databases, which may have partly confounded our data.

In summary, we found that a parental history of T1D was associated with a 29% increased risk of being diagnosed with ADHD in offspring. The underlying mechanisms need to be explored in further studies.

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