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Association of attention-deficit/hyperactivity disorder with diabetes: a population-based study

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BACKGROUND: Cognitive impairment has been documented in adult diabetes but is unclear in pediatric diabetes. No study had been conducted to explore the relationship between attention-deficit/hyperactivity disorder (ADHD) and diabetes. Using a population-based data set, we aimed to examine the association between ADHD and a prior diagnosis of diabetes mellitus (DM) in Taiwan.

METHODS: A total of 4,302 patients with ADHD were selected as cases and 21,510 randomly selected subjects as controls. We used conditional logistic regression to calculate the odds ratio (OR) for having previously received a diagnosis of DM between subjects with and without ADHD.

RESULTS: In this study, 116 of the 25,812 sampled subjects (0.5%) had received a diagnosis of DM prior to their index date. Subjects with ADHD had a higher proportion of prior DM diagnoses than controls (0.9% vs. 0.4%, $P < 0.001$). After adjusting for age, sex, index year, geographic location, and obesity, ADHD was significantly associated with a prior diagnosis of type 2 DM (OR = 2.75, 95% confidence interval (CI) = 1.82–4.16). However, no significant association was observed between ADHD and type 1 DM.

CONCLUSION: The findings suggest that ADHD was associated with a previous diagnosis of type 2 DM.

Attention-deficit/hyperactivity disorder (ADHD) is the most common cognitive and behavioral disorder diagnosed among schoolchildren and adolescents, with an estimated prevalence of 5.29% (1). The pathophysiology of ADHD is marked by dopaminergic and nonadrenergic dysregulation, as well as by structural and functional abnormalities of the cortico-cortical and fronto-subcortical pathways, including those of the striatum and cerebellum (2). The etiology of ADHD is multifactorial and generally stems from a combination of genetic and acquired factors. Various biological and environmental factors, including viral infection (3), lead contamination (4), maternal smoking during pregnancy (5), alcohol exposure (6), prematurity (7), low birth weight (8), and nutritional and thyroid disorders (9), may contribute to its development. However, it is still not clear whether diabetes mellitus (DM) is a risk factor for the development of ADHD among children.

The effects of DM on the central nervous system have been emphasized recently. In studies conducted among school-aged children, those with early-onset DM have been shown to demonstrate poorer academic achievement, visual spatial ability, memory, motor speed, and eye–hand coordination (10,11). Type 2 DM, known as a common disorder in adulthood, is dramatically increasing in both children and adolescents, in relation to increased incidence of obesity (12). Some psychiatric disorders, such as depression and behavior disorders, are reported to be increased in patients with type 2 DM (13,14). It has been suggested that chronic hyperglycemia at an early age increases neuronal vulnerability (15,16) and may impede myelination of the developing brain (17). The results of animal and human case studies suggest that hypoglycemia may induce cell death in the brain, possibly through excitotoxic or apoptotic processes (18,19). However, although both chronic hyperglycemia and recurrent episodes of hypoglycemia may lead to central nervous system damage, the long-term effects of DM on the central nervous system are still controversial (20,21). To the best of our knowledge, no study has attempted to explore the association between ADHD and DM. Therefore, using a population-based data set, we aimed to examine the association between ADHD and prior DM diagnosis in Taiwan.

RESULTS

This study included 4,302 newly diagnosed subjects with ADHD and 21,510 matched controls. Of the 25,812 sampled subjects, the mean age was 8.6 y (SD = 2.7 y). **Table 1** shows the distribution of demographic characteristics between subjects with and without ADHD. After matching for age and sex, subjects with ADHD were found to more likely be residents of the northern part of Taiwan ($P < 0.001$) than subjects without ADHD.

Table 2 presents the prevalence of prior diabetes between subjects with and without ADHD. It shows that 116 of the 25,812 sampled subjects (0.5%) were diagnosed with diabetes prior to the index date. Subjects with ADHD had a higher proportion of prior diabetes as compared with subjects without ADHD (0.9 vs. 0.4%, $P < 0.001$). We further analyzed the prevalence of type 1 DM and type 2 DM between subjects with and without ADHD. We found that subjects with ADHD had a

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Received 17 April 2012; accepted 21 October 2012; advance online publication 27 February 2013. doi:10.1038/pr.2013.5

Table 1. Demographic characteristics of patients with attention-deficit/hyperactivity disorder and controls in Taiwan in the years 2002–2008 ($N = 25,812$)

	Patients with attention-deficit/hyperactivity disorder ($n = 4,302$)		Controls ($n = 21,510$)		
Variable	Total no.	%	Total no.	%	*P* value
Age (years)					1.000
5	474	11.0	2,370	11.0	
6	627	14.6	3,135	14.6	
7	755	17.6	3,775	17.6	
8	578	13.4	2,890	13.4	
9	469	10.9	2,345	10.9	
10	391	9.1	1,955	9.1	
11	278	6.5	1,390	6.5	
12	247	5.7	1,235	5.7	
13	232	5.4	1,160	5.4	
14	168	3.9	840	3.9	
15	83	1.9	415	1.9	
Sex					1.000
Male	3,442	80.0	17,210	80.0	
Female	860	20.0	4,300	20.0	
Geographic region					<0.001
Northern Taiwan	2,473	57.5	10,040	46.7	
Central Taiwan	737	17.1	5,446	25.3	
Southern Taiwan	997	23.2	5,514	25.6	
Eastern Taiwan	95	2.2	510	2.4	
Obesity	23	0.5	56	0.3	0.003

Table 2. Prevalence for prior diabetes among the sampled patients

	Total ($N = 25,812$)		Patients with attention-deficit/hyperactivity disorder ($n = 4,302$)		Controls ($n = 21,510$)	
Variable	*n*	%	*n*	%	*n*	%
Presence of diabetes						
Yes	116	0.5	40	0.9	76	0.4
Presence of type 1 diabetes						
Yes	16	0.1	4	0.1	12	0.1
Presence of type 2 diabetes						
Yes	100	0.4	36	0.8	64	0.3

higher prevalence of type 2 DM than subjects without ADHD (0.8 vs. 0.3%, $P < 0.001$). However, there was no significant difference in the prevalence of type 1 DM between subjects with and without ADHD (0.1 vs. 0.1%, $P = 0.371$).

Table 3 shows the crude and covariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for ADHD. Conditional logistic regression suggested that ADHD was significantly related to type 2 DM (OR = 2.83, 95% CI = 1.88–4.26) but not type 1 DM (OR = 1.68, 95% CI = 0.54–5.20). Furthermore,

Table 3. Crude and covariate-adjusted ORs for attention-deficit/hyperactivity disorder among the sampled patients ($N = 25,812$)

	Attention-deficit/hyperactivity disorder	
Variable	Crude OR (95% CI)	Adjusted OR (95% CI)
DM		
Type 1	1.68 (0.54–5.20)	1.62 (0.51–5.14)
Type 2	2.83† (1.88–4.26)	2.75† (1.82–4.16)
No (reference group)	1.00	1.00
Age (years)		
5 (reference group)	1.00	1.00
6	1.00 (0.88–1.14)	1.00 (0.88–1.14)
7	1.00 (0.88–1.13)	1.00 (0.88–1.14)
8	1.00 (0.88–1.14)	0.99 (0.87–1.14)
9	1.00 (0.87–1.15)	1.01 (0.87–1.15)
10	1.00 (0.86–1.16)	1.00 (0.86–1.16)
11	1.00 (0.85–1.18)	1.01 (0.86–1.18)
12	1.00 (0.85–1.18)	1.01 (0.86–1.18)
13	1.00 (0.85–1.19)	1.00 (0.85–1.19)
14	1.00 (0.83–1.21)	1.00 (0.84–1.23)
15	1.00 (0.78–1.29)	1.01 (0.79–1.32)
Index year		
2002 (reference group)	1.00	1.00
2003	1.00 (0.87–1.13)	1.01 (0.88–1.14)
2004	1.00 (0.86–1.16)	1.01 (0.88–1.16)
2005	1.00 (0.87–1.14)	1.00 (0.87–1.13)
2006	1.00 (0.89–1.10)	1.01 (0.87–1.16)
2007	1.00 (0.86–1.16)	0.99 (0.86–1.16)
2008	1.00 (0.87–1.17)	1.00 (0.87–1.18)
Sex		
Male	1.00 (0.92–1.09)	0.99 (0.92–1.08)
Female (reference group)	1.00	1.00
Obesity	2.16** (1.26–3.71)	1.98* (1.15–3.40)

CI, confidence interval; DM, diabetes mellitus; OR, odds ratio.
*$P < 0.05$; **$P < 0.01$; †$P < 0.001$.

after adjusting for age, sex, index year, geographic location, and obesity, ADHD was significantly associated with prior type 2 DM (OR = 2.75, 95% CI = 1.82–4.16). However, no significant association was detected between ADHD and type 1 DM.

DISCUSSION

In this investigation, we found type 2 DM to be associated with ADHD after adjusting for potential confounding factors. To the best of our knowledge, this is the first study to demonstrate this association. The pathogenesis of type 2 DM is quite different from that of type 1 DM. Type 2 DM is primarily caused by insulin resistance on target tissues and relative insulin deficiency, whereas type 1 DM is mainly caused by insulin deficiency due to the autoimmune-mediated destruction of pancreatic β cells (22). The incidence of type 2 DM due to obesity and associated insulin resistance in childhood and

adolescence is dramatically increasing. It is estimated that up to 45% of all DM reported in childhood and adolescence is type 2 DM (12,23). Although there is significant emerging literature regarding the adverse effects of type 2 DM on the central nervous system in middle-aged and elderly individuals (24–26), there is little information available regarding this effect among the pediatric group. Adults with type 2 DM have been found to have decreasing white matter volumes, especially in the frontal area, and cortical/subcortical atrophy (27,28). The impairment of cognitive function in patients with type 2 DM has also been demonstrated to be correlated to the reduced circulation of the frontal and parietal lobes (29). The hippocampus and frontal area are regions responsible for attention, cognition, and motor planning. Damage to these regions may lead to inattention, loss of emotion, behavioral inhibition, and poor memory.

ADHD is characterized by impairments in attention, motor, and emotion regulation. According to various neuroimaging and functional studies, the core of the attention network includes the lateral and medial prefrontal cortices, the lateral-inferior parietal and temporo-occipito-parietal cortices in the surface of the right hemisphere (30,31), and the circuits of the cortico-striatal and cortico-cerebellar networks. These subserve motor, cognitive, and emotional behaviors (32). Type 2 DM most commonly affects the frontal and hippocampus regions, which may explain the risk for developing ADHD symptoms later.

Of interest, type 1 DM was not shown to be significantly associated with ADHD in our study. Rovet and Alvarez (33) have reported that attentional cognitive processes are disrupted in children and adolescents with type 1 DM, but no other study has been conducted investigating the correlation of executive symptoms, the core symptom of ADHD, with DM. One possible reason is that type 1 DM and type 2 DM demonstrate different pathophysiologies of insulin regulation. Type 2 DM is characterized by insulin resistance on target tissues such as the brain. Altfas (34) reported that ADHD was highly prevalent among obese patients and highest in those with extreme obesity. Bruehl *et al.* (35) reported that adolescents with type 2 DM with insulin resistance have significantly reduced hippocampal and prefrontal volumes and higher rates of global cerebral atrophy as compared with obese controls without insulin resistance. Insulin and insulin receptor signaling play a modulatory role in learning and memory processing (36). The role of hyperinsulinemia and abnormalities in insulin signaling within the brain need to be studied because they might explain some of the apparent differential effects of type 1 diabetes and type 2 diabetes on the brain.

The primary strength of our study lies in its population-based database and large sample population, which mitigate the effect of the selection biases inherent in studies utilizing data taken from voluntary registries and hospital-referred study patients. However, this study suffered from several limitations that should be addressed. The first is the use of International Classification of Disease, 9th edition (ICD-9) coding in the administrative database to diagnose ADHD and DM. Because of this we were unable to include any measure of severity of ADHD and DM in this investigation. Second, the Longitudinal Health Insurance Database (LHID2005) lacks information on prenatal, perinatal social, parental psychopathological variables, and body weight information that have been reported to be associated with ADHD (37). Third, surveillance bias could have been a potential limitation if patients with DM were more likely to be screened for ADHD. However, this study found that ADHD was associated only with type 2 DM, not type 1 DM. This accordingly discounts the possibility that receiving medical attention for DM contributed to elevated odds of developing ADHD. Finally, although we have controlled for comorbid psychotic and mood disorders, sometimes ADHD behaviors are extreme enough that a physician may prescribe an antipsychotic medication. As these medications have been suggested to contribute to diabetes, it is possible that their use influenced the results of this study. This avenue of investigation should be further explored in future studies (38).

In conclusion, our report suggests that type 2 DM in childhood is associated with ADHD. Type 2 DM is a chronic medical condition with an increasing childhood and adolescent incidence, during crucial times for brain development. ADHD is a neurological disorder with high risk of adverse personal and social outcomes. Early identification of children at risk for ADHD among patients with DM is necessary to ensure that they receive prompt and appropriate treatment. Primary physicians should provide routine screening for ADHD in addition to routine primary diabetic management.

METHODS

Database

The data for this study were sourced from the LHID2005. The LHID2005 was created and released to the public by the National Health Research Institute and includes all the original claim data and registration files for 1,000,000 individuals randomly sampled from the 2005 Registry for Beneficiaries (n = 25.68 million) of the National Health Insurance program. The Taiwan National Health Research Institute has validated the representativeness of the LHID2005 relative to the whole population of National Health Insurance enrollees according to gender distribution, age distribution, and average insured payroll-related amount. The LHID2005 provided an exclusive opportunity for researchers to trace all the medical utilizations of these 1,000,000 enrollees since the inauguration of the National Health Insurance program.

Because the LHID2005 consists of de-identified secondary data released to the public for research purposes, this study was exempted from full review by the Taipei Medical University Institutional Review Board.

Selection of Cases and Controls

This study was designed as a case–control study. The case–control study is frequently contrasted with cohort studies, in which exposed and unexposed subjects are observed until they develop an outcome of interest. Therefore, this study did not study the incident cases of DM, and the precise causal relationship between ADHD and DM cannot be determined by the case–control study. We selected 5,554 patients aged between 5 and 15 y who received a first-time diagnosis of ADHD (ICD-9-Clinical Modification (CM) (39) code 314.00 or 314.01) in their ambulatory care visits between January 2002 and December 2008). To increase the diagnostic validity of the subjects with ADHD in this study, we included only those cases who had received ≥3 ADHD diagnoses. In Taiwan, the first diagnosis of a condition reflects the clinician's utilization of a diagnostic test to assess the condition in

question, whereas the second diagnosis indicates the presence of the condition based on the outcome of both the diagnostic test and a clinical examination. Therefore, by limiting our cases to those who received ≥3 ADHD diagnoses, we assured that all of our cases received a positive diagnosis based on their symptoms, medical history, and the results of at least one diagnostic test. We excluded patients who had been diagnosed with preterm births (ICD-9-CM codes 765.00–765.09, 765.10–765.19) or low birth weight (ICD-9-CM codes V21.30–V21.35) (n = 820), which have been reported to be risk factors for ADHD (7,8). In addition, we excluded patients who had been diagnosed with a congenital anomaly (ICD-9-CM codes 758.0–758.9, 759.9) (n = 41). We further excluded subjects who had been diagnosed with mental illness (ICD-9-CM codes 290–319, except 314.01) (n = 20).We also excluded patients who had received a diagnosis of cerebral palsy, intracranial hemorrhage, viral encephalitis, hypoxic–ischemic encephalitis, epilepsy/seizure, or thyroid disorder (n = 371). Ultimately, 4,302 patients with ADHD were selected as cases. We assigned the date of their first diagnosis of ADHD as the index date.

We likewise selected five controls for each ADHD case, based upon the principles provided by Hennessy *et al.* (40), from the remaining enrollees of the LHID2005. A total of 21,510 controls were selected. These controls were frequency-matched with cases by age, sex, and index year. We assured that none of the selected controls had ever been diagnosed with any type of mental illness, preterm birth, low birth weight, congenital anomaly, cerebral palsy, intracranial hemorrhage, viral encephalitis, hypoxic–ischemic encephalitis, epilepsy/seizure, or thyroid disorder. For controls, we assigned their first use of ambulatory care occurring in the index year as their index date.

Exposure Assessment

We identified diabetes cases based on ICD-9-CM code 250 (22). To increase the diagnostic validity of diabetes, we included only patients who had at least two consensus diabetes diagnoses. Furthermore, this study included diabetes cases only if the diabetes diagnosis was made before the index date.

Statistical Analysis

We used SAS system (SAS System for Windows, Version 8.2; SAS Institute, Cary, NC) for the statistical analyses. We first compared the distributions of the geographic location of the community in which the patient resided (northern, central, eastern, or southern Taiwan) between cases and controls using (^{2} tests. We used logistic regression (conditioned on age, sex, and index year) to explore the relationship between diabetes and ADHD. In the regression models, we also adjusted for age, sex, index year, geographic region, and obesity (ICD-9-CM codes 278, 278.0, 278.00, and 278.01). In this study, although we identified obesity cases by ICD-9-CM codes, obesity for children (aged 2–19) is defined as a body mass index at or above the 95th percentile for children of the same age and sex in Taiwan. A P value of ≤0.05 was used to assess statistical significance in this study.

ACKNOWLEDGMENTS

This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, Taiwan and managed by the National Health Research Institutes. The interpretations and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health, or the National Health Research Institutes.

Disclosure: The authors declared no conflict of interest.

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