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Research Article / Araştırma Makalesi

Is there a Relation Between Type 1 Diabetes Mellitus and ADHD and Severity of ADHD in Children and Adolescents? A Case-Control Study

Çocuk ve Ergenlerde Tip 1 Diyabetes Mellitus ile DEHB ve DEHB Şiddeti Arasında Bir İlişki Var mı? Vaka Kontrol Çalışması

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Abstract: Our aim in this study was to investigate the relation between type 1 diabetes mellitus (DM) and attention deficit-hyperactivity disorder (ADHD) and severity of ADHD in children and adolescents. Cases (n:80) and healthy children (n:80) aged 6-18 and followed-up with Type 1 DM were included in the study. Psychiatric evaluation in the light of DSM-5 (The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition diagnostic criteria), an information form, the ADHD section of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (6-18) (K-SADS-PL-T), the DuPaul ADHD Rating Scale, the Conners Teaching Rating Scale (CTRS), and the Conners Parental Rating Scale (CPRS) was applied to the participants. The two groups were compared in terms of ADHD and ADHD severity. Sixteen of the cases with type 1 DM, and 5 of the control group were diagnosed with ADHD, the rate of ADHD being higher in the case group (chi-square $p<0.05$). A statistically significant difference was determined between the ADHD scale scores. Mean HbA1c in cases diagnosed with ADHD in the case group was higher than in undiagnosed cases ($p=0.020$). All scale parameters, apart from HbA1c and the attention part of the CTRS, were higher in cases diagnosed with ADHD in the case group than in cases not diagnosed with ADHD($p=0.020$). Duration of exposure to diabetes, and numbers of hospitalizations and ketoacidosis attacks were higher in cases with ADHD in the case group than in those without ADHD ($p<0.05$). There was a significant difference in terms of ADHD between the control and case groups in our study, and there is a probable association between ADHD and type 1 DM. Further, more detailed studies are needed to provide a clear explanation of that relation.
Keywords: type 1 Diabetes Mellitus, Attention Deficit-Hyperactivity Disorder, ADHD Severity, Child and Adolescent

Özet: Çalışmamızda çocuk ve ergenlerde tip 1 diyabetes mellitus (DM) ile dikkat eksikliği hiperaktivite bozukluğu (DEHB) ve DEHB şiddetiyle ilişkinin araştırılmasını amaçladık. Çalışmaya 6-18 yaş arası, tip 1 DM tanısı ile takip edilen olgular hastalar(n:80) ve sağlıklı çocuklar(n:80) alındı. Katılımcılara DSM-5(Amerikan Psikiyatri Birliği Ruhsal Bozuklukların Tanısal ve istatistiksel El Kitabı'nın beşinci baskısı) tanı ölçütlerinin göz önünde bulundurulduğu psikiyatrik değerlendirme, bilgi formu, Okul Çağı Çocukları (6-18) için Duygulanım Bozuklukları ve Şizofreni Görüşme Çizelgesi - Şimdi ve Yaşam Boyu şekli - Türkçe Uyarlamasının(ÇDŞG-ŞY-T) DEHB ile ilgili kısmı, DuPaul DEHB ölçeği, Conners Öğretmen Derecelendirme Ölçeği(CÖDÖ) ve Conners aile Derecelendirme Ölçeği (CADÖ) uygulandı. İki grup DEHB ve DEHB şiddeti açısından karşılaştırıldı. Tip 1 DM'li tanılı hastalarınolguların 16'sı, kontrol grubundan ise 5'i DEHB tanısı aldı ve vaka grubunda DEHB tanısı oranı daha yüksek çıktı (Ki-Kare $p<0,05$). DEHB ölçek puanları arasında istatistiksel olarak anlamlı farklılık bulundu. OlguVaka grubunda DEHB tanısı alanların HbA1c ortalamaları, almayanlara göre daha yüksekti ($p=0,020$). OlguVaka grubunda DEHB'li tanısı alanların HbA1c ile CÖDÖ dikkat kısmı dışındaki tüm ölçek puan parametreleri, DEHB tanısı almayanlara göre daha yüksek bulundu ($p=0,020$). OlguVaka grubunda DEHB'li olanların, olmayanlara göre diyabete maruz kalma süreleri, hastaneye yatış diyabet tanısı ile geçirilen süre, hastaneye yatış sayısı ve ketoasidoz atak sayıları daha fazlaydı ($p<0.05$). Çalışmamızda DEHB tanısı açısından kontrol ve olguVaka grupları arasında anlamlı fark vardı ve DEHB ile tip 1 DM arasında bir ilişki olması muhtemeldir. Bu ilişkinin net bir şekilde açıklanabilmesi için daha ayrıntılı ve ileri çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Tip 1 Diyabetes Mellitus, Dikkat Eksikliği Hiperaktivite Bozukluğu, HbA1c, DEHB Şiddeti, Çocuk ve Ergen

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1. Introduction

Attention deficit-hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by symptoms of difficulty in maintaining attention, hyperactivity, and impulsivity. The reported prevalence is 5-10% (1), and it is 3-5 times more common in boys than in girls. Various hypotheses have been proposed to account for this, but the reason is still unclear (2). Interactions between genetic, biological, and environmental factors are currently regarded as being implicated in the etiology of ADHD. Studies of ADHD have suggested that neurotransmitters play a significant role, and that the dopaminergic system is particularly involved in the etiology. Studies of environmental factors have largely concentrated on causes adversely affecting brain development. These have indicated causes such as viral infection, thyroid disorders, and various biological factors, as well as maternal smoking during pregnancy, exposure to alcohol, prematurity, low birth weight, and nutrition as factors leading to ADHD (3).

Diabetes mellitus (DM) is a carbohydrate, fat, and protein metabolism disorder developing as a result of insufficient or inefficient insulin release. It is the most common endocrine-metabolic disease in childhood and adolescence, and the third most common chronic disease in children after asthma and cerebral palsy (4, 5). The estimated prevalence of type 1 DM in school-age children and adolescents is approximately 0.2% (6). Type 1 DM represents 10-15% of all diabetics (7). It can be seen at all ages, but insulin-dependent DM is more a disease of childhood and adolescence (7). Furthermore, an increased risk of ADHD was observed in children with type 1 DM, but not in their healthy siblings, which suggests the existence of a diabetes-related casual factor in ADHD (8). Studies on the effect of DM on the central nervous system have suggested that both chronic hyperglycemia and recurrent hypoglycemia attacks may cause central nervous system damage. Weak glycemic control has been shown to have an adverse effect on brain functions and structure in patients with type 1 DM (9). In terms of brain structure, hypoglycemia has particularly been reported to lead to damage in neurons in the medial temporal region, also including the hippocampus (9). Attention and cognition, one of the principal functions of the hippocampus, are also known hallmarks of ADHD (10). Type 1 DM is associated with severe hypoglycemia in early childhood, together with deficiencies in motor and visual-spatial functioning, and subsequently in memory and attention. In addition, slow gray and white matter growth has been reported in association with hyperglycemia in the rapid brain maturation process in children with type 1 DM (11). Another study showed slower growth rates of cortical volume and total surface area associated with hyperglycemia in the brains of children with type 1 DM (12). These findings are reported to impose restrictions on the frontal brain networks in particular and to cause inadequate development of executive functions (9). In agreement with the above studies, a thinner cortex in the region of the right and left postcentral gyrus has been determined in children aged 6-8 with intensive attention and hyperactivity problems (13). School-aged children with early-onset diabetes were observed to have poor academic performance, visual-spatial ability, motor speed, and eye-hand coordination (14). In addition to being an organic disease, DM can affect patients in psychosocial terms, and adjustment disorders, including symptoms of anxiety and depression, secondary to complications, tests and treatment methods may develop (4). We developed the hypotheses of a potential relation between type 1 DM and ADHD due functional changes in the brain caused by hypo/hyperglycemia corresponding closely to ADHD symptoms. The purpose of this study was to investigate the relations between type 1 DM and ADHD and the severity thereof in children and adolescents by comparing these with a non-diabetic control group.

2. Materials and Methods

In this study, we planned to assess 80 cases with type 1 DM under monitoring by the Erzurum Regional Training and Research Hospital Pediatric Endocrinology Polyclinic

and 80 healthy children and adolescents presenting to the Healthy Child Observation Polyclinic and with no identified pathology in terms of ADHD. We also planned to compare patients with type 1 DM and healthy children and adolescents in terms of ADHD in a blinded manner.

Children and adolescents aged 7-18 and agreeing to take part were enrolled in the study. Subjects diagnosed with pervasive developmental disorder or mental retardation (an IQ test (Stanford-Binet) was applied to all children included in the study, and those with IQ<70 were excluded), not aged 7-18 years or unwilling to take part, patients in the case group with any additional pathology other than type 1 DM, and subjects in the control group with any disease were excluded from the study. In addition, none of the children in our study were obese, their percentile values ranging between 3 and 85. The case and control group members and their families were informed about the study, and informed consent forms were obtained from those agreeing to take part. The study was approved by the Erzurum Regional Training and Research Hospital ethical committee (No. 2015/14-126). The study was performed between October 2017 and October 2018.

Severity of ADHD in children diagnosed with the condition was investigated in detail using symptoms in DSM-5 (information obtained from interviews with children and families, and from teachers). During that analysis these symptoms were classified as low, high and very high. Cases with generally low symptoms were classified as mild ADHD, those with more symptoms as moderate, and those with very many as severe, and these classifications were supported by the scales administered. Sociodemographic data (age, sex, education, premorbid characteristics) were elicited from parents before the assessment. The patient and parents were interviewed, and children also underwent face-to-face psychiatric interviews. The section of the the Turkish version of the Kiddie Schedule for Affective Disorders and Schizophrenia– Present and Lifetime Version for School-Age Children (6-18) (K-SADS-PL-T) (15) related to ADHD was applied to all participants. This is administered by interviewing the parents and child, and assessment is based on information received from all sources. Parents were interviewed prior to the enrolment of children and adolescents. Parents in the case and control groups were asked whether they had been diagnosed with and/or treated for ADHD. In the event of any inconsistency between information received from the different sources, the author used his clinical judgment. K-SADS-PL was developed from K-SADS-P by Kaufman et al. (1997), who reported that KSADS-PL is a valid and reliable diagnostic scale (16).

DuPaul ADHD Rating Scale

This 18-item scale contains one item for each of the 18 symptoms in the diagnosis of ADHD in DSM-IV. The scale was developed by Du Paul et al. (1998) and assesses the severity of symptoms during the previous week. The scale is scored by experienced personnel in the research center based on interviews with parents and patient, albeit not together (17).

Conners Teacher Rating Scale (CTRS)

This scale was developed by Conners to assess students' behaviors in class (18). The form has been adapted to Turkish culture (19).

Conners Parental Rating Scale (CPRS)

This four-point Likert-type scale was developed to evaluate children's behavior within the family. The Turkish-language version was produced by Şener et al. (1998) (20).

Statistical analysis

Our study was initially arranged in the form of 80 cases and 80 controls with no power analysis. At the end of the study, the test power was calculated at 73.5% using the two-tail test, and the alpha error level or confidence level was set at 5%. Descriptive statistics were used to describe constant variables (mean, standard deviation, minimum, median, and maximum). Student's t test was used to assess relations between two independent and normally distributed constant variables. Relations between categorical

variables were determined using the chi-square test (or Fisher's Exact test where appropriate). Relations between two independent and non-normally distributed variables were examined using the Mann-Whitney U test. Statistical significance was set at a level of 0.05. Analyses were performed on MedCalc Statistical Software version 12.7.7 (MedCalc Software BVBA, Ostend, Belgium; http://www.medcalc.org; 2013).

3. Results

One hundred sixty children were included in the study, 80 in the type 1 DM group and 80 in the non-DM group. No statistically significant difference was observed between the two groups in terms of sociodemographic characteristics (Table 1).

The type 1 DM group consisted of 35 girls and 45 boys, and the control group of 35 girls and 45 boys. Sixteen members of the type 1 DM group and five of the control group were diagnosed with ADHD. Two of the children diagnosed with ADHD were regarded as severe on the basis of DSM-5 diagnostic criteria, nine as moderate, and five as mild. In the control group, one patient was diagnosed with severe ADHD, one with moderate ADHD and one with mild ADHD. The prevalence of ADHD was higher in the case group than in the control group.

A statistically significant difference was determined at comparison of mean HbA1c values in the cases with ADHD and those without ADHD in the case group (p=0.020). Mean HbA1c values were significantly higher in the cases diagnosed with ADHD (Table 2).

When the patients with and without ADHD were compared in the case group, number of hospitalizations, number of ketoacidosis attacks, and duration of exposure to diabetes were identified as statistically significant ($p<0.05$). Numbers of hospitalizations and ketoacidosis attacks and duration of exposure to diabetes were all higher in the ADHD group (Table 2).

Table 1. A comparison of sociodemographic characteristics of the case and control groups

	Type 1 DM	Control	p
Numbers in the groups (n)	80	80	
Sex (female)	35 (43.75)	35 (43.75)	1.00*
Sex (male)	45 (56.25)	45 (56.25)	1.00*
Age (mean years±SD)	10.68 ±2.6	10.16 ±2.1	0.166**
Maternal age (mean years±SD)	38.6 ±3.6	39.2 ±3.3	0.273**
Paternal age (mean years±SD)	41.1 ±2.7	42.1 ±3.8	0.056**
Maternal education(mean years±SD)	5.7 ± 5.52	5.5 ±3.1	0.778**
Paternal education(mean years±SD)	8.2 ±4	7.7 ±3.2	0.384**
Number of siblings (mean±SD)	1.7±1.3	1.5±1	0.277**
Parents separated	8 (10%)	7 (8.9%)	0.974*
Families with ADHD in at least one parent	8 (10%)	7 (8.9%)	0.974*

*chi-square p. **Student's t p

Table 2. Comparison of duration of exposure to diabetes, hospital stays, numbers of ketoacidosis attacks and HbA1c levels in subjects among subjects with ADHD in the case group.

Type 1 DM	ADHD 16/80	No ADHD64/80	p
HbA1c mean	8.8±2.5	7.4±1.3	0.020
Length of exposure to diabetes (years)	4.5±1.6	3.14±1.19	0.0318
Number of hospitalizations	1.75±0.77	1.01±0.48	0.0174
Number of ketoacidosis attacks	0.75±0.57	0.39±0.49	0.0433

Mann-Whitney U

4. Discussion

In addition to genetic components, biological and environment factors also occupy an important place in the etiology of ADHD. Due to the neuroanatomical and neuropsychological effects of hypoglycemia and hyperglycemia, and the fact that these effects correspond to some cerebral changes in ADHD, our study investigated the relation between type 1 DM and ADHD. We determined that ADHD was more prevalent in cases of type 1 DM than in the controls, and that cases if type 1 DM diagnosed with ADHD had poorer glycemic control than type 1 DM cases without ADHD. Although ADHD frequentlya ccompanied specific learning difficulty and depression and anxiety disorders, we were unable to investigate this relation in detail since it was beyond the scope of the present study.

The prevalence of psychiatric disease is reported to be 2-3-fold higher in adolescents and young adults with type 1 DM than in the general population (21). Psychiatric diagnoses in adolescents and young adults with type 1 DM vary among studies, although most report a high incidence of multiple psychiatric diseases (22). Studies of the effect of diabetes on ADHD have largely focused on the relation between type 2 diabetes and obesity, and an association with ADHD has also been proposed (2,23). The number of studies investigating the link between type 1 DM and ADHD in children is limited. Some of these studies have reported no link between ADHD and type 1 DM, while others have suggested that type 1 DM leads to attention problems (2,24). However, some studies have employed only hospital databases, while other have investigated ADHD from all angles, and have not performed a detailed investigation. None of the subjects in our study were obese. We also excluded patients with type 2 DM from the control group, enrolling only those with type 1 DM. Our aim was to compare these with healthy volunteers with no disease to determine whether there is any relation between ADHD and type 1 DM.

The human brain requires a constant supply of glucose to meet its energy needs. Glucose deprivation therefore results in rapid cognitive dysfunction (25). The structures primarily linked to memory functions are the frontal and medial temporal lobes, and particularly the hippocampus (26). Observational studies have identified the cerebral cortex and hippocampus as the regions most sensitive to damage due to hypoglycemic episodes (9, 11). Research has confirmed that diabetes is linked to neuroanatomical differences compared to the healthy population and has established that these differences may be affected by disease-associated factors including hypoglycemic episodes and age of onset of the disease (11). One study comparing young adults with type 1 DM with healthy subjects reported significantly larger lateral ventricles and dilated subarachnoid spaces in the cerebral vault and cerebellum resulting from atrophy in diabetic individuals (27). Studies have also determined significantly less gray matter volume in the superior temporal/occipital cortex in young people with type 1 DM with a history of severe hypoglycemia compared to patients with type 1 DM without severe hypoglycemic episodes. Exposure to hyperglycemia exposure has been linked to differences in both gray and white matter volumes, decreased gray matter volume in the posterior cortical areas and decreased white matter volume in the right superior parietal area (28). A history of hypoglycemic episodes has also been linked to deficits in a wide range of cognitive domains, such as motor, visuospatial, attention, memory, and executive functioning. Significantly higher blood glucose levels have also been reported in adolescents with diabetes than in diabetic adults. This “threshold effect” would seem to imply that individuals may be more sensitive to a decrease in blood glucose levels while the brain is still in the process of development (28).

There are also studies suggesting that diabetes may be associated with poor impulse control in addition to attention deficit. In the studies, it has been shown that the medial prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, ventromedial prefrontal cortex, amygdala play an important role in shaping impulsivity and aggression. Individuals with ventromedial prefrontal cortex damage exhibit higher impulsivity than healthy individuals

(29). Diabetes can trigger diseases with a common neuroendocrine structure, such as poor impulse control and over-eating, by damaging these areas of the brain or by affecting the physiology of the brain (30). Therefore, while impulsivity leads to poor sugar control, weak sugar control can also trigger impulsivity.

Our intention in this study was to examine the relation between type 1 DM and ADHD and the severity thereof in children and adolescents by comparing these with a non-diabetic control group. In our study, when the type 1 DM group and the control group were compared, the rate of ADHD was high in the case group. This is likely to have an adverse effect on cognitive functions by affecting the central nervous system of type 1DM. It has been suggested that hyper / hypoglycemic episodes have more destructive effects on cognitive functions and may cause more attention problems. In agreement with these studies, we observed that patients diagnosed with ADHD had worse blood glucose control in the case group. In our study, attention deficit subtype of ADHD was higher in the case group. This suggests that diabetes, especially bad blood sugar control, may be associated with ADHD, especially attention problems. The high number of hospitalizations and ketoacidosis attacks in the patients who were diagnosed with attention deficit in the case group indicates the non-compliance of the patients with diet and treatment. This suggests that diet incompatibility and poor blood sugar control are not only related to impulsivity, but also attention deficit may be associated with poor blood glucose control and dietary mismatch. It is possible that children with attention deficit do not comply with the diet and treatment due to the presence of symptoms such as lack of attention, quickly becoming bored, forgetfulness, refusal to comply with plans etc. Hypo/hyperglycemic attacks in cases of type 1 DM may closely resemble inattention symptoms in association with their hippocampal and cortical effects and may impair patients' executive functions (6). Executive functions are compromised in patients with ADHD, and this can make it difficult to establish blood sugar control in patients with type 1 DM. ADHD and type 1 DM may thus have had two-way adverse inpacts on one another.

Type 1 DM patients with poor blood sugar control have a higher probability of hypoglycemic and hyperglycemic attacks. Attention deficit is particularly evident in children with type 1 DM, and especially those with a history of hypoglycemia, in tasks requiring attention or focusing (29). One study assessing attention control and intelligence in 103 diabetic children and 100 healthy controls showed that the attention skills of the diabetic children differed from and were lower than those of the controls (24). Kapellen et al. also demonstrated a higher prevalence of ADHD in children with type 1 DM than in those without type 1 DM (2.9% vs. 2.4%) (31) Furthermore, an increased risk of ADHD was observed in children with T1DM, but not in their healthy siblings, which suggests the existence of a diabetes-related casual factor of ADHD. Another study evaluated diabetic children with a history of hypoglycemia, comparing these with non-hypoglycemic diabetics and non-diabetic controls. The authors reported that findings for visual and auditory attention indicated that participants with a history of hypoglycemia scored lower than non-hypoglycemic diabetics and normal controls, although the difference was not statistically significant (32).

Although the prevalence of ADHD in the case group in our study was higher than that in the control group, further, more detailed studies are needed to account for this relationship. Patients with type 1 DM must be followed-up, subjected to clinical evaluation during follow-up, and administered tests and scales. Factors such as attention and performance should be compared with previous assessments during this process. Additionally, numbers of hospitalization and ketoacidosis attacks, and HbA1c values were higher in patients diagnosed with ADHD compared to those in diabetics with no diagnosis of ADHD. This may derive from diabetic patients with ADHD neglecting diet and treatment. Questions that need to be answered are therefore whether diabetes leads to ADHD or affect the severity of ADHD, or whether lack of attention to diet and treatment of diabetic patients with ADHD leads to poor blood sugar control.

One of the principal limitations of our study concerns the sample size. A larger sample size would have permitted an evaluation of other variables, particularly in the ADHD group. Another limitation is that additional vital findings were not established in the case group. We think that the inclusion of these parameters in future studies will be useful in determining vital findings capable of affecting the relation under investigation.

In conclusion, ADHD was more prevalent in cases with type 1 DM than in the controls. In addition, hyperactivity scores were lower and inattention scores were higher in ADHD cases with accompanying type 1 DM compared to those without accompanying type 1. The reason for this difference needs to be clarified in future studies. In addition, glycemic control was in diabetic cases with ADHD compared t those without ADHD. Therefore, if patients with type 1 DM are also diagnosed with ADHD during the therapeutic process, they should also be closely followed-up in terms of glycemic control. Further studies are now needed to clarify the relation between ADHD and type 1 DM, considering also the effect of environmental factors in the etiology of ADHD.

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