Original article / *Araştırma*

An evaluation of attention deficit hyperactivity disorder and specific learning disorder in children born to diabetic gravidas: a case control study

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ABSTRACT

Objective: *Children born after risky pregnancies are known to have an increased disposition to neurodevelopmental disorders. The purpose of our study was to investigate the relationship between diabetic pregnancy and attention deficit hyperactivity disorder (ADHD) and specific learning disorder (SLD).* ***Methods:*** *One hundred thirty-seven children of mothers with diabetic pregnancies and 128 children of mothers without a history of diabetic pregnancy were enrolled. Forty-nine of the case group had a history of insulin-dependent diabetes mellitus (IDDM) and 88 of gestational diabetes mellitus (GDM). All participants were evaluated using The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (6-18) (K-SADS PL), the Wechsler Intelligence Scale for Children-Revised (WISC-R), and the SLD Battery. The results were then subjected to statistical analysis.* ***Results:*** *A statistically significant difference was determined between the case and control groups in terms of levels of diagnosis of ADHD and SLD. Significant differences were determined between verbal/performance/total IQ scores when IDDM and GDM were compared with the control group. When the IDDM and GDM subgroups were compared among themselves, no significant difference was determined between verbal/performance/total IQ scores. Significant variation was observed between the IDDM and GDM groups in terms of ADHD and SLD diagnoses. IQ scores decreased as fasting blood sugar increased in all parameters.* ***Conclusion:*** *Significantly, more diagnoses of ADHD and SLD were observed in children born to diabetic mothers compared to those of non-diabetic mothers. Further, wide-ranging studies on the subject of the effect of diabetic pregnancy and blood sugar control on infant neurodevelopmental disorders are now needed.* ***(Anatolian Journal of Psychiatry 2019; 20(4):442-448)***

Keywords: *attention deficit hyperactivity disorder, specific learning disorder, diabetic pregnant, mental health, child, neurodevelopmental disorders*

Diyabetik gebelerden doğan çocukların dikkat eksikliği hiperaktivite bozukluğu ve özgül öğrenme güçlüğü açısından değerlendirilmesi: Olgu kontrol çalışması

ÖZ

Amaç: *Riskli hamileliklerden doğan çocuklarda nörogelişimsel bozukluklara eğilimin arttığı bilinmektedir. Çalışmamızda diyabetik gebelik ile dikkat eksikliği hiperaktivite bozukluğu (DEHB) ve özgül öğrenme güçlüğü (ÖÖG) arasındaki ilişkiyi araştırmayı amaçladık.* ***Yöntem:*** *Bu çalışmaya, annelerinde diyabetik gebeliği olan 137 çocuk ile*

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annesinde diyabetik gebelik öyküsü olmayan 128 çocuk alındı. Olgu gurubunda 49 katılımcının insüline bağımlı diyabetes mellitus (İBDM), 88 katılımcının gestasyonel diyabetes mellitus (GDM) öyküsü vardı. Tüm katılımcılar, Okul Çağı Çocukları için Duygulanım Bozuklukları ve Şizofreni Görüşme Çizelgesi-Şimdi ve Yaşam Boyu Şekli (6-18) (K-SADS PL), Wechsler Çocuklar için Zeka Testi (WISC-R), ÖÖG Bataryası ile değerlendirildi. Elde edilen sonuçlar istatistiksel olarak karşılaştırıldı. ***Bulgular:*** *Olgu ve kontrol grupları arasında DEHB ve ÖÖG tanısı oranları arasında istatistiksel olarak anlamlı fark vardı. İBDM ve GDM ile kontrol grubu karşılaştırıldığında sözel/performans/ toplam IQ puanları arasında anlamlı fark saptandı. İBDM ve GDM kendi içlerinde karşılaştırıldığında sözel/performans/toplam IQ puanları arasında anlamlı fark saptanmadı. IDDM ve GDM grupları arasında DEHB ve ÖÖG tanıları arasında anlamlı fark olduğu görüldü. Tüm parametrelerde açlık kan şekeri (AKŞ) arttıkça IQ puanlarında düşüş olduğu görülmüştür* ***Sonuç:*** *Diyabetik gebelerden doğan çocuklarda DEHB ve ÖÖG tanılarının diyabetik olmayan gebelerden doğan çocuklara göre daha fazla olduğu görüldü. Diyabetik gebeliğin ve kan şekeri kontrolünün, bebeklerin nörogelişimsel bozukluklar üzerine etkisi konusunda daha geniş kapsamlı çalışmalara gerek vardır.* ***(Anadolu Psikiyatri Derg 2019; 20(4):442-448)***

Anahtar sözcükler: *Dikkat eksikliği hiperaktivite bozukluğu, özgül öğrenme bozukluğu, diyabetik gebe, ruh sağlığı, çocuk, nörogelişimsel bozukluklar*

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by difficulty in maintaining attention, hyperactivity and impulsivity symptoms. The reported prevalence is 5-10%.[1] It is 3-5 times more common in boys than in girls. Although various theories have been proposed to account for the greater incidence in boys, the reason is still unclear. Specific learning disorder (SLD) is a neurodevelopmental and neurobiological disorder frequently seen in childhood and leading to function impairment in one or more areas.[2] The incidence is 3-4 times higher in boys than in girls.[3] SLD and ADHD may be comorbid. Germano et al. reported SLD and ADHD comorbidity at 30-50%.[4] Studies have suggested that ADHD and SLD may be linked by genetic interaction.[5,6] Psychosocial and environmental factors may be important in the progression of both diseases.[7] The relation between ADHD and reading disability in particular among learning difficulties is lined to shared congenital factors, and studies have reported that it is important, when the two conditions are co-present, for both to be evaluated in terms of treatment.[4,7] Disturbances that affect the baby in pregnancy and delivery (such as asphyxia, infection, and toxic-metabolic-mechanical disturbances) may cause minimal damage in the infant brain and function impairment. Accompanied by neurological soft signs, this functional impairment has been reported to be capable of causing ADHD[8-10] and SLD.[11,12]

Diabetes mellitus (DM) in pregnancy occurs in three forms; pre-existing type 1 diabetes (existing before pregnancy), type 2 diabetes existing before pregnancy, and gestational diabetes (initial diabetes or first diagnosis during pregnancy).[13] Research has shown that gestational diabetes accounts for the great majority of diabetic pregnancies (87%), type 1 diabetes for an additional 7% and type 2 diabetes for 5%.[13,14] The estimated prevalence of pregnancy-related DM is 5%.[14] Malformation has been determined in 8-8.6% of babies with diabetic mothers and in 3.8% of babies with non-diabetic mothers.[15] Perinatal complications in diabetic pregnancies include macrosomia, hypoglycemia, respiratory distress syndrome, polycythemia, hypobilirubinemia, cardiomyopathy, congenital anomalies and sudden infant death.[16] Maternal diabetes in pregnancy is also thought to be capable of affecting the child's cognitive development in association with neonatal complications.[17] Maternal diabetes in pregnancy may also affect long-term cognitive ability due to altered brain structure caused by intrauterine metabolic changes and fetal neurodevelopmental development.[18] Although the IQ test scores of children born to diabetic mothers are not completely affected, minor neurological damage may persist. Alternatively, neurological damage may already exist but may manifest in neuropsycholo-gical abilities at later ages among previously investigated individuals.[19]

Although individual differences make the decision difficult, children born from high-risk pregnancies have a tendency to developmental delay, learning difficulties in school and a high rate of ADHD.[20] We therefore investigated whether there is any relation between diabetic pregnancies and ADHD and SLD.

METHODS

In this study, we aimed to compare children born to diabetic and non-diabetic pregnancies who delivered at Atatürk University Faculty of Medicine between 2005 and 2010 in terms of SLD and ADHD. The families of the children identified were contacted by telephone, and the study was

explained to them. One hundred thirty-seven families with a history of diabetic pregnancy and 128 families with no such history agreed to take part. Families agreeing to participate were invited, together with their children, to the Child and Adolescent Mental Health and Diseases Clinic, where children underwent psychiatric evaluation. Children aged 6-12 years whose families agreed to participate were included in the study. Children diagnosed with another neurodevelopmental disorder, born before 37 weeks (preterm), or with a history of head trauma were excluded. The study content was explained to the case and control groups and their families, and signed informed consent forms were obtained from those agreeing to take part. The interviewer performing the evaluation was blinded to whether the mothers of the children attending had experienced diabetic pregnancies. The consent form that was filled by parents was in accordance with the Declaration of Helsinki as amended by the World Medical Association Declaration of Helsinki (World Medical Association, 2013). The study was approved by the Atatürk University, Medical Faculty Ethics Committee (No. 121, dated 2017).

Thirty of the diabetic subjects were under monitoring with a diagnosis of type 1 diabetes and 19 with a diagnosis of type 2 diabetes, while GDM was determined in 88 mothers. We learned that the mothers diagnosed with IDDM presented with polyuria, polydipsia and weight loss, and had transient or permanent glycosuria. These were diagnosed with type 1 and 2 diabetes with a history of metabolic acidosis, with or without coma, and there were still mothers being follow-up from that perspective. Diagnosis of GDM was based on two or more positive values according to Carpenter-Coustan's criteria (95, 180, 155, and 140 mg/dl) at the 100 g oral glucose tolerance test (OGTT),[21] file reviews and histories taken from mothers. Participating children were assessed by the experienced child psychiatrist according to the DSM-5 criteria for ADHD and SLD. In addition, the following evaluations have been made.

Children attending the polyclinic were administered the Turkish language version of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (6-18) (K-SADS PL). The validity and reliability of the Turkish-language version were established by Gökler et al.[22]

Learning Disabilities Symptom Checklist (LDSC): This was developed by Korkmazlar and is based on a questionnaire used at the Developmental Center in London, a diagnostic and therapeutic center for children with learning disability.[23]

Wechsler Intelligence Scale for Children-Revised (WISC-R): This test was developed by Wechsler in 1949, and revised in 1974. It was adapted to Turkish conditions by Savaşır and Şahin in 1986.[24]

RESULTS

Eighty-eight of the diabetic pregnancies in our study were diagnosed as gestational diabetes, and forty-nine as IDDM. Sixty-five of the 137 children born to diabetic gravidas, were girls and seventy-two were boys, while sixty-three of the children born to normal gravidas were girls and sixty-five were boys. Mean age at time of delivery among the diabetic gravidas was 29.8 years, compared to 29.2 in the control group. ADHD was diagnosed in 32 (23.36%) of the 137 children born to diabetic gravidas (seven girls, 25 boys), SLD in 22 (16.06%) (six girls, 16 boys), and ADHD+SLD in 11 (8.03%). ADHD was diagnosed in nine (7.03%) of the 128 volunteers in the control group (three girls, six boys), SLD in eight (6.25%) (two girls, six boys) SLD, and ADHD+SLD in 4 (3.12%). Statistically significant differences were determined in levels of ADHD and SLD between the case and control groups ($p<0.001$, $p=0.011$, respectively) (Table 1). Significant differences were also determined between the case and control groups in terms of verbal/performance/total IQ scores ($p<0.001$). No significant difference was determined between the case and control groups in terms of age and sex distributions ($p=0.118$, $p=0.773$, respectively). No significant difference was also determined in terms of mothers' ages in the case and control groups ($p=0.511$) (Table 1).

Forty-nine subjects in the case group were from the IDDM subgroup and 88 from the GDM subgroup. We compared the groups' IQ scores with fasting blood sugar (FBS) values. The highest IQ scores were determined in the control group. We also determined a statistically significant difference between the gestational diabetes group and the control group in terms of verbal/performance/total IQ scores ($p<0.001$). Comparison of the insulin-dependent diabetes (type 1 and 2 diabetes) group and the control group revealed a significant difference in terms of verbal/performance/total IQ scores ($p<0.001$). When the GDM and IDDM groups were com-

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

		Case		Control		
		Number	%	Number	%	p*
Total		137	51.7	128	48.3	
Male		72	52.6	65	50.8	0.773**
Female		65	48.4	63	49.2	
ADHD		32	23.3	9	7.0	<0.001**
SLD		22	16.0	8	6.2	0.011**
Age	Mean±SD	8.5±1.4		8.2±1.5		0.118*
	Median	9.00		8.00		
Mother's age	Mean±SD	29.8±6.1		29.2±6.2		0.511*
	Median	28		28		
Verbal IQ	Mean±SD	101.0±4.5		105.0±3.1		<0.001*
	Median	102		106		
Performance IQ	Mean±SD	104.7±2.3		108.2±1.2		<0.001*
	Median	105		108		
Total IQ	Mean±SD	102.8±1.9		106.5±1.6		<0.001*
	Median	103.5		107		

**: Mann Whitney U test; **: Chi-square test; SLD: Specific Learning Disorder; ADHD: Attention Deficit Hyperactivity Disorder; IQ: Intelligence Quotient, percentage of rows*

pared between themselves, we observed no significant difference in verbal/performance/total IQ scores (p=0.162, p=0.933, p=0.029, respecttively) (Table 2).

ADHD was diagnosed in 18 of the 49 children born to gravidas with IDDM, SLD in 13, and SLD+ADHD in seven, and in 14 of the 88 children born to gravidas with GDM, SLD in nine and SLD+ADHD in four (Table 2). A statistically significant difference was determined between the GDM and IDDM groups in terms of diagnoses of ADHD and SLD (p<0.001*, p=0.012*, respectively) (Table 2).

The mean HbA1c value in the 49 infants with diabetic mothers (IDMs) with IDDM was 6.4±0.6, and the mean HbA1c value in 88 IDMs with GDM was 5.8±0.7 (p<0.001). Correlation analysis was performed in order to analyze the relation between IQ scores and FBS. Inverse correlation was determined between total IQ score and FBS values at a level of 0.438 (43.8%). This indicates a weak correlation. A weak inverse correlation

Table 2. Comparison of group IQ scores compared to the diabetic controls

		GDM		IDDM		Control				
		Number	%	Number	%	Number	%	p1	p2	p3
Total		88	64.2	49	35.8	128	100.0			
ADHD	Yes	14	15.9	18	36.7	9	7.0	0.001*	0.115*	<0.001*
	No	74	84.1	31	63.3	119	93.0			
SLD	Yes	9	10.2	13	26.5	8	6.2	0.012*	0.566*	<0.001*
	No	79	89.8	36	73.5	120	93.8			
HbA1c		5.8±0.7		6.4±0.6		-		<0.001*		
Verbal IQ	Mean±SD	101.9±3.1		99.7±6.1		105.0±3.1		0.162	<0.001	<0.001
	Median	102.0		102.0		106				
Performance IQ	Mean±SD	104.6±1.8		104.8±3.1		108.3±1.2		0.933	<0.001	<0.001
	Median	105.0		105.0		108				
Total IQ	Mean±SD	103.2±1.5		102.3±2.4		106.6±1.6		0.029	<0.001	<0.001
	Median	103.5		103.0		107				

**: Mann Whitney U test, Chi-square test; p1: GDM-IDDM; p2: GDM-control; p3: IDDM-control, †Percentage of column*

Table 3. Blood sugar and total IQ score correlation analysis

	Pearson's correlation	p
Total IQ - FBS	-0.438	<0.001
Verbal IQ - FBS	-0.368	<0.001
Performance IQ - FBS	-0.258	<0.001

IQ: Intelligence Quotient; FBS: Fasting blood sugar

was also determined between verbal IQ and FBS values at 0.368 (36.8%). Weak correlation was also observed between performance IQ and FBS values at 0.258 (25.8%). A decrease was observed in IQ scores as FBS increased in all parameters (Table 3).

DISCUSSION

Although several studies have investigated the relation between diabetic pregnancy and ADHD (25-28), to the best of our knowledge no previous studies have investigated the relation with SLD. This study evaluated ADHD and SLD, important neurodevelopmental disorders, and IQ scores in school-age children of diabetic mothers, and also investigated relations with PGDM and GDM. We investigated relations between the IDDM and GDM subgroups and ADHD, SLD and IQ, and performed comparisons with healthy controls. We also investigated the relation between FBS and IQ scores.

Increased and fluctuating circulating glucose levels and ketonemia in diabetic gravidas have been reported to be capable of resulting in developmental changes in organs and systems in offspring and adverse perinatal outcomes such as alteration in brain development and hypoglycemia.[13,18] Although some studies have shown that exposure to maternal pregnancy has a positive effect on cognitive ability in chil-dren,[13,29,30] negative associations have also been determined between maternal pregnancy glycated hemoglobin (HbA1c) levels[31] and pregnancy fasting blood glucose levels of insulin-treated diabetic mothers and offspring cognitive ability.[32]

The positive effect of maternal diabetes on cognitive abilities may be associated with good control of diabetes in diabetic mothers during pregnancy. In agreement with these last two studies[31,32] we determined an inverse correlation, albeit a weak one, between verbal, performance and total IQ and FBS levels of mothers with diabetic pregnancies. Although, in contrast to these findings, one recent study determined no relation between maternal glucose intolerance in early pregnancy and neurodevelopment in children aged four,[33] it should be remembered that some neurodevelopmental disorder may not be clinically identified until the age of 12.

Low verbal IQ scores have been observed in school-age children of mothers with GDM.[25] Low IQ scores have also been determined in children of mothers with PGDM and acetonuria.[34] In agreement with these studies, we determined lower verbal, performance and total IQ scores using the WISC-R in the children of mothers with diabetic pregnancies compared to the control group. In contrast to these findings, normal cognitive functions at IQ evaluation using the WISC-R have also been determined in studies comparing school-age children of well-controlled diabetic mothers and healthy.[35,36] In addition, one review also reported normal cognitive performance in the children of mothers with GDM.[24] However, in our study, verbal, performance and total IQ scores were significantly lower in the GDM group compared to the healthy control group. Moreover, total IQ scores were lower in the IDDM than in the GDM group, while we determined no statistically significant difference in verbal or performance IQ scores.

ADHD has been shown to be more common in the children of mothers with GDM,[25-28] while a higher rate of inattention is seen in children of mothers with GDM or PGDM.[36] One very recent study reported no increased risk of ADHD in adolescent children of mothers with type 1 DM (assessed using the Conners' Continuous Performance Test II), although self-reported use of ADHD medication was higher compared with a healthy control group.[37] The use of existing ADHD drugs may therefore have prevented detection of ADHD through the test performed. In our analysis using a structured method (KSADS-PL), ADHD was significantly higher in children from diabetic pregnancies compared to the controls. In addition, there was a statistically significant difference in terms of ADHD between children born from IDDM diabetic (type 1 and 2) gravidas compared to children with GDM. Poorer cognitive function and a higher frequency of learning difficulties have been observed in adolescent offspring of mothers with type 1 diabetes, and these adolescents have been reported to experience difficulties with mathematics at elementary school.[31] Other studies have also reported an increase in learning difficulties.[25,27,35,36] In the present study, we analyzed SLD using the LDSC. In agreement with other studies, SLD was

significantly higher in the children of mothers with diabetic pregnancies compared to the control group. These findings emphasize the importance of blood sugar being kept under control during diabetic pregnancy.

However, the study also has some limitations. One major limitation is that the research was performed in a limited region. Generalizing the study to society in general may therefore be problematic. In addition to diabetic pregnancy, various problems deriving from other risky pregnancies may result in learning disability and ADHD by causing minimal brain damage. We investigated only diabetes in pregnant women, and other risk factors need to be assessed and clarified in order to overcome this deficiency. Another limitation is that we do not know whether environmental factors after birth give rise to learning disability and ADHD. Clarification of other environmental factors can resolve this limitation. Genetic factors may also increase disposition to learning disability and ADHD. Children born from diabetic pregnancies may be genetically disposed to learning disability and ADHD. Another limitation of our study is that we did not investigate genetic and familial disposition in the children from the diabetic pregnancy and control groups. In addition, in the socioeconomic status evaluation of the patients, the health center is a hospital where patients are referred at every socioeconomic level due to the fact that it is the tertiary center. In conclusion, further studies involving larger groups from different surroundings, and investigation of other risk factors in pregnancy and environmental factors after birth and genetic effects are now needed in order to overcome these limitations.

Our study findings show that the neurodevelopmental disorders ADHD and SLD were more common in children of mothers with diabetic pregnancies, and that ADHD and SLD were more prevalent in children of mothers with IDDM compared to children of mothers with GDM. This indicates that blood sugar elevation in children exposed to high blood sugar from the first stage of pregnancy and/or gravidas with IDDM can increase the risk of ADHD and SLD. Lower IQ scores were determined in the children of mothers with diabetic pregnancy. Control of DM during pregnancies will contribute to preventing not only perinatal complications, but also the development of neurodevelopmental disorders. Our findings and the existing literature clearly show that further more comprehensive studies investigating diabetic pregnancy and neurodevelopmental disorders are now needed.

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