ARAŞTIRMA / RESEARCH

The Relationship Between Maternal Chronic Disease, Infection, and Having a Child with Autism Spectrum Disorder

Maternal Kronik Hastalık ve Enfeksiyon ile Otizm Spektrum Bozukluğu Olan Çocuğa Sahip Olma Arasındaki İlişki

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Geliş tarihi/Received: 25.01.2022
Kabul tarihi/Accepted: 10.10.2022

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Abstract

Objective: The aim of the study was to evaluate the relationship between prenatal chronic diseases, infection, and autism spectrum disorder.

Material and Method: Retrospective, cross-sectional and comparative research design was used. The sample was conducted with 99 mothers for the group, 44 of whom had a child with autism spectrum disorder and 55 of whom had a child with non-autism spectrum disorder. Data were collected from mothers between October 2020 and January 2021 via online methods (Facebook, Whatsapp, and Instagram). The study data was collected with a questionnaire form and the Childhood Autism Rating Scale.

Results: It was determined that autism spectrum disorder was more common in the children of mothers with maternal diabetes (χ^2= 5.196; p= 0.023) and infection (χ^2= 5.331; p= 0.021). Gender, low birth weight, and twin pregnancy were also found to be risk factors for autism (p<0.05).

Conclusion: As a result, the data obtained show that chronic diseases and infection of the mother in the prenatal period increase the risk of autism in the child. Therefore, in the presence of diseases such as maternal diabetes and infections, the mother and fetus should be monitored, and children with autism spectrum disorders should be detected at an early stage.

Keywords: Autism spectrum disorder, chronic diseases, infection, maternal.

Öz

Amaç: Bu çalışmanın amacı, maternal kronik hastalıklar ve enfeksiyon ile otizm spektrum bozukluğu olan çocuğa sahip olma arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Retrospektif, kesitsel ve karşılaştırmalı araştırma tasarımı kullanılmıştır. Örneklem otizm spektrum bozukluğu olan çocuğa sahip 44, otizm dışı spektrum bozukluğu olan çocuğa sahip 55 olmak üzere 99 anne ile yürütülmüştür. Veriler çevrimiçi yöntemle (Facebook, Whatsapp and Instagram) Ekim 2020 - Ocak 2021 tarihleri arasında annelerden toplanmıştır. Çalışma verileri anket formu ve Çocukluk Çağı Otizm Derecelendirme Ölçeği ile toplanmıştır.

Bulgular: Maternal diyabeti (χ^2= 5,196; p= 0,023) ve enfeksiyonu bulunan (χ^2= 5,331; p= 0,021) annelerin çocuklarında daha fazla otizm spektrum bozukluğu görüldüğü belirlenmiştir. Ayrıca cinsiyet, düşük doğum ağırlığı ve ikiz gebeliğin de otizm için risk faktörleri olduğu bulunmuştur (p<0,05).

Sonuç: Sonuç olarak, elde edilen veriler annenin doğum öncesi dönemde sahip olduğu kronik hastalıklar ve enfeksiyonun, çocukta otizm görülme riskini artırdığını göstermektedir. Bu nedenle maternal diyabet ve enfeksiyon gibi hastalıkların varlığında anne ve fetüs izlenmeli, otizm spektrum bozukluğu olan çocuklar erken dönemde tespit edilmelidir.

Anahtar Kelimeler: Enfeksiyon, kronik hastalıklar, maternal, otizm spektrum bozukluğu.

1. Introduction

Autism spectrum disorder (ASD) is a prevalent heterogeneous group of neurodevelopmental disorders characterized by deficits in socialization and communication and by repetitive or unusual behaviors (1). The prevalence of ASD has dramatically increased over the past decade (2).

According to the Centers for Disease Control and Prevention (CDC), approximately 1 in 54 children suffer from ASD in the United States (3). The prevalence of childhood ASD was 1 per 100 in Taiwan (4). In Turkey, although there is no definite data regarding the prevalence of ASD, it is stated that the number of children diagnosed with ASD at the age of compulsory education is 16.837 and 53.2% of special education and rehabilitation centers provide education to children with ASD (5). Although the complex etiology of ASD remains largely unknown, it is estimated that the development of ASD is associated with a sophisticated collection of both genetic and environmental variables (6,7). And also, several studies implicated the prenatal term as a sensitive period for the development of ASD (7-9). Early fetal growth, especially brain overgrowth, is one of the most striking phenomena in ASD (9). So, numerous prenatal factors such as maternal infection and maternal diseases are proposed as drivers of increased risk (10,11).

Maternal diabetes and hypertension are the most common complications of pregnancy. It is possible that both conditions affect fetal brain growth (6). The negative effects of maternal diabetes on the brain may result from

intrauterine increased fetal oxidative stress, epigenetic changes of several genes, and other unknown causes (10). There are several hypotheses that maternal hypertension may affect fetal neurodevelopment. Oxidative stress and inflammation due to hypertension have also been associated with changes in fetal neurodevelopment. Hypertensive disorders are also associated with altered fetal nutrient delivery and intrauterine development restriction (6,12).

One of the significant risk factors for ASD is the adverse intrauterine environment resulting from maternal bacterial and viral infections (10). A significant association between intrauterine inflammation, infection, and ASD is found in numerous studies (2,11,12-14).

This study was conducted to provide data lacking in the literature. There is no study that considered both maternal chronic diseases and infection as risk factors for autism spectrum disorder at the same time and examined the relationship between them. The aim of this study is to determine the relationship between maternal chronic diseases (diabetes and hypertension), infection, and ASD.

Primary healthcare workers, particularly Maternal and Child Health Nurses can play an integral role in the detection, early implementation of treatment, and effective management of chronic diseases among mothers. This study will contribute to the awareness that pregnant women with chronic diseases and infections in the maternal period are at risk for ASD and should receive health care accordingly.

2. Material and Methods

2.1. Research Design and Sample

The study was a retrospective, cross-sectional and comparative type. The research population consisted of mothers aged between 26-48 and children with ASD and non-ASD diagnoses. The individuals who participated in the research were selected according to the simple random sampling methodology. Considering the degree of confidence (95%), the margin of error (5%), effect size (0.5), and the ability test (80%), the sample size was determined as 40 women for each group. The sample included 99 participants divided into two groups. The first group was composed of mothers of 44 autistic children previously identified. The second group was composed of mothers of 55 non-autistic children. The two groups included children aged between 3 and 10 years. Participants were recruited by using social media applications (Facebook, Whatsapp, and Instagram).

The inclusion criteria were as follows: willingness to participate, having children with ASD (for the ASD group) or non-ASD (for the non-ASD group), and being over the age of 18. Patients who were illiterate, have language barriers, and who did not want to be included in the study for any reason were excluded from the study.

2.2. Data Collection

The study data was collected with an interview form with 55 (for the non-ASD group) and 44 (for the ASD group) questions conducted by the researchers to collect information about participants' demographic, obstetric, and child information. To determine the autistic behavior Childhood Autism Rating Scale (CARS) was used for the ASD group.

Childhood Autism Rating Scale (CARS): CARS was developed by Schoppler et al. in 1980. CARS, consisting of 15 items; is a behavioral rating scale developed to distinguish between children with intellectual disability (ID) without autistic symptoms and children with autistic symptoms. The 15 items in the scale are relating to people, imitative behavior, emotional response, body use, object use, adaptation to change, visual response, listening response, perceptive response, fear or anxiety, verbal communication, non-verbal communication, activity level, level and consistency of intellective relations, general impressions. A score between 1 and 4 for each item: 1 indicates appropriate behavior for the age level and a serious deviation from normal behavior for the age level is 4. The total score can be a minimum of 15 and a maximum of 60. According to the scoring, it was classified that the child as not autistic (below 30), mild or moderately autistic (30–36.5), or severely autistic (above 36.5) (Schoppler et al. 1980). The validity and reliability study of the scale in the Turkish language was made by İncekaş Gassaloğlu et al. in 2016. The Cronbach's alpha of the CARS in the Turkish version was 0.95. The Cronbach's alpha of the CARS in this study was 0.92.

CARS scoring can be done during the clinical interview, with in-class observation, information obtained from parents, and file records (İncekaş Gassaloğlu et al. 2016). In this study, the data was collected from parents with online methods between October 2020 - January 2021. The questionnaire form was uploaded to Google Forms and advertised on social media applications (Facebook, Whatsapp, and Instagram). Before Google Forms was sent to each participant, it was arranged so that only one response was provided for each participant in the study. The questionnaire was advertised in many different cities in Turkey.

2.3. Ethical Considerations

Ethics committee approval was obtained from the Noninvasive Clinic Ethical Committee of a university (30.12.2020 protocol no: 54674167-050.01.04-206) in Turkey. Before starting the answering questionnaire, consent was obtained. The study was conducted in accordance with the Declaration of Helsinki and verbal permission of the mothers who voluntarily participated in the research was obtained.

2.4. Data Analysis

Statistical Package for Social Sciences (SPSS) (Windows 15.0) software was used for data analysis. Descriptive statistical methods (mean, standard deviation, frequency, minimum and maximum) were used for statistical analysis of data, and Mann Whitney U and Chi-squared tests were calculated for determining the relationship between the descriptive tests, groups, and scale. All tests were conducted with $p<0.05$.

3. Results

Ninety-nine mothers participated in the research. Table 1 shows the comparison of maternal factors in ASD and non-ASD groups. It was found that there was no statistically significant difference between the two groups in age, maternal age at conception, child age, gestational age at birth, labor and delivery time at vaginal birth, and maternal weight gain ($p>0.05$). The rate of boys was higher in the ASD group (86.4%) than non-ASD group (60.0%) and the difference was statistically significant ($\chi^2= 8.376$; $p= 0.004$).

Table 1. Comparison of Prenatal Factors in Two Groups

Characteristics	ASD (n=44)		non-ASD (n=55)			
	$\bar{X}$ ± SD	Min-Max	$\bar{X}$ ± SD	Min-Max	Z_{mwu}*	p**
Age	33.75±5.87	26-48	32.25±5.00	22-49	-0.715	0.475
Maternal age at conception	29.43±5.26	17-39	28.73±4.97	20-48	-1.348	0.178
Child age	5.04±2.16	3-10	4.41±1.92	3-10	-1.916	0.055
Gestational age at birth	37.77±2.99	27-41	38.72±2.07	32-42	-1.440	0.150
Labor and delivery time at vaginal birth	5.40±5.34	1-24	8.47-7.51	1-32	-0.358	0.720
Maternal weight gain	20.22±16.13	5-27	20.27±18.67	6-28	-0.533	0.594

Characteristics		ASD (n=44)		non-ASD (n=55)					
		n	%	n	%	χ^2***	p**	OR****	95% CI
Gender	Boy	38	86.4	33	60.0	8.376	0.004	4.22	1.52-11.66
	Girl	6	13.6	22	40.0				
Maternal smoking	Yes	5	11.4	1	1.8	3.912	0.085	6.92	0.77-61.62
	No	39	88.6	54	98.2				
Plurality	Singleton	39	88.6	55	100.0	6.582	0.015	0.88	0.79-0.98
	Multiple	5	11.4	0	0.0				
Birth Type	Vaginal Birth	22	50.0	23	41.8	0.660	0.417	1.39	0.62-3.08
	Cesarean Birth	22	50.0	32	58.2				
Oxytocin induction at vaginal birth	Yes	14	63.6	12	52.2	0.327	0.567	1.27	0.55-2.95
	No	8	36.4	11	47.8				
Pre-pregnancy BMI	≤18.5 kg/m² (low weight)	4	9.1	6	10.9	7.458	0.059		
	18.6-24.9 kg/m²(normal weight)	26	59.1	43	78.2				
	25-29.9 kg/m²(overweight)	12	27.3	4	7.3				
	≥ 30 kg/m²(obese)	2	4.5	2	3.6				
Birth Weight	≤2500 gr (Low birth weight)	8	18.2	3	5.5	7.048	0.029		
	2501-4000 gr (Normal birth weight)	19	43.2	37	67.3				
	≥4001 gr (Macrosomia)	17	38.6	15	27.3				

ASD: Autism Spectrum Disorder, BMI: Body Mass Index, Min: Minimum, Maks: Maksimum, SD: Standart Deviation, CI: Confidence Interval, *Z_{MWU}= Mann Whitney U, **p<0.05 ***χ^2: Chi-squared ****OR: Odds Ratio

Table 2. Comparison of Diabetes, Hypertension and Infection in Pregnancy in Two Groups

Characteristics		ASD (n=44)		non-ASD (n=55)					
		n	%	n	%	χ^2**	P*	OR***	95% CI
Diabetes in pregnancy	No	38	86.4	54	98.2	5.196	0.023	2.52	1.98-6.73
	Yes	6	13.6	1	1.8				
Type of diabetes	Gestational diabetes	6	100.0	1	100.0	1.090	0.332	2.01	0.53-7.63
	Prepregnancy diabetes	0	0.0	0	0.0				
Hypertension in pregnancy	No	42	95.5	51	92.7	0.319	0.690	0.60	0.10-3.47
	Yes	2	4.5	4	7.3				
Type of hypertension	Gestational hypertension	2	100.0	4	100.0	0.319	0.690	0.60	0.10-3.47
	Prepregnancy hypertension	0	0.0	0	0.0				
Infection in pregnancy	No	30	68.2	48	87.3	5.331	0.021	3.20	1.15-8.83
	Yes	14	31.8	7	12.7				
Type of infection	Urinary tract infection	7	50.0	4	57.1	75.038	0.000		
	Genital tract infection	3	21.4	2	28.5				
	Respiratory infections	4	28.6	1	14.4				

ASD: Autism Spectrum Disorder, CI: Confidence Interval, *p<0.05, **χ^2: Chi-squared, ***OR: Odds Ratio

While there was no multiple pregnancies in non-ASD group; it was determined that 11.4% of the pregnancies were multiple in ASD group (n=5). It was found that there was a statistically significant difference between birth weight in groups (χ^2= 7.048; p= 0.029).

Table 2 shows the comparison of diabetes, hypertension, and infection in pregnancy in two groups. The 13.6% (n=6) of the ASD group had diabetes in pregnancy while the 1.8% (n=1) of the non-ASD group had diabetes in pregnancy and the difference was statistically significant (χ^2= 5.196; p= 0.023). It was found that there was a statistically significant difference between ASD (31.8%, n=14) and non-ASD (12.7%, n=7) groups in infection in pregnancy (χ^2= 5.331; p= 0.021). There was no statistically significant difference between the two groups in hypertension (p>0.05).

Table 3 shows the results of the Childhood Autism Rating Scale (CARS) in the ASD group. According to the CARS 47.7% of the children were as not autistic (n=21), 22.7% of the children were mild or moderately autistic (n=10) and 29.5% of the children were severely autistic (n=13).

Table 3. The Results of Childhood Autism Rating Scale in Autism Spectrum Disorder Group

Scale	ASD (n=44)		
	X ± SD	Min	Max
Childhood Autism Rating Scale	31.79±9.81	15	60
	n	%	
Child as not autistic (<30.0)	21	47.7	
Mild or moderately autistic (30.0-36.5)	10	22.7	
Severely autistic (>36.5)	13	29.5	

ASD: Autism Spectrum Disorder, Min: Minimum, Maks: Maksimum, SD: Standart Deviation

Table 4 shows the relationships between prenatal factors and CARS. There was no statistically significant difference between diabetes and infection in pregnancy and CARS (p>0.05). It was found that there was a statistically significant difference between gender and CARS (χ^2= 4.757; p= 0.039).

4. Discussion

The relationship between maternal chronic diseases, infection, and autism spectrum disorder was examined as well as some prenatal characteristics, that could be considered as risk factors for ASD. There was no difference between ASD and non-ASD groups in age, maternal age at conception, child age, and gestational age at birth.

Confirming previous studies, the rate of boys was found higher in the ASD group in this study. The ratio was about 4:1 male to female. The epidemiological studies suggested that the ratio in prevalence may be in the range of 2–5:1 male to female (17-19) Wang et al. (20) found that the rate of boys was higher in ASD. Similarly, Galvan et al. (21) indicated that the boy gender in ASD was higher than non-ASD. It was determined that male fetuses typically suffer more neurologic dysfunction in comparison to females following gestation complications associated with asphyxia (22). Considering that asphyxia increases the risk of ASD (23), the higher rate of boy gender can be explained accordingly.

In this study low birth weight (LBW) was found as a risk factor for ASD. A common explanation for the association between LBW and ASD is that LBW is a marker of prematurity. Prematurity is a determinant risk factor for fetal growth and well-being, and it can affect fetal brain growth (24,25). In the study of Hadjkacem et al. (26), LBW was found as a risk factor for ASD. Chien et al. (7) also found that the LBW ratio was higher in the ASD group compared to non-ASD group.

According to some studies, gestational diabetes is mainly associated with an increased risk for ASD (7,12,26). Gestational diabetes disturbs fetal growth and increases the rate of a variety of pregnancy complications (26). Gestational diabetes exposes the fetus to an environment where nutrients and neuroendocrine agents like triglycerides, fatty acids, glucose, and leptin are higher. The most immediate effect of this is fetal hyperglycemia. As glucose can cross the blood-placenta barrier while maternal insulin cannot, the fetus secretes its own insulin, which is also a growth factor for brain development. Thus, it has been hypothesized that hyperinsulinemia in the prenatal period might lead to a change in brain development. In addition to insulin, leptin also increases. Leptin receptors are distributed among several brain regions which play a central role in behavioral regulation (27). The negative effects of maternal diabetes on the brain may also result from intrauterine increased fetal oxidative stress and epigenetic changes in the expression of various genes. Oxidative stress may damage to neurodevelopment of the fetus (26). In this study, maternal diabetes ratio was about 2.5:1 ASD to non-ASD, and the difference was statistically significant (Table 2). In the study of Chien et al. (7) and Hadjkacem et al. (26), maternal diabetes was found as a risk factor for ASD.

The one of most important maternal risk factors for ASD is maternal infection. Maternal infection has teratogenic

Table 4. The Relationship Between Prenatal Factors and Childhood Autism Rating Scale

Characteristics		ASD (n=44)							
		Child as not autistic (<30.0)		Mild or moderately autistic (30.0-36.5)		Severely autistic (>36.5)		χ^{2**}	p*
		n	%	n	%	n	%		
Diabetes in pregnancy	**Yes**	3	50.0	1	16.7	2	33.3	0.154	0.926
	No	18	47.4	9	23.7	11	28.9		
Infection in pregnancy	**Yes**	6	42.9	2	14.3	6	42.9	5.615	0.060
	No	15	50.0	8	26.7	7	23.3		
Gender	**Boy**	20	52.6	9	23.7	9	23.7	4.757	0.039
	Girl	1	16.7	1	16.7	4	66.7		

ASD: Autism Spectrum Disorder,*p<0.05, **χ^2 Chi-squared

effects on the fetus and damages the central nervous system. The presence of maternal infection during pregnancy significantly increases the risk of ASD (2). Among women who had an infection during pregnancy, an increased risk of ASD was reported for any infection in each trimester. Especially, viral infection in the first trimester and bacterial infections in the second trimester, or bacterial infection in the third trimester, and genitourinary infections during the third trimester were also associated with ASD (14). In this study, a statistically significant relationship was found between infection and ASD. The ratio was 3.2:1 ASD to non-ASD.

In this study, according to the results of CARS in the ASD group, the majority of them (47.7%) were as not autistic behavioral. This may be because the results were obtained based on the mother's observation. According to the results of the study, it was determined that diabetes and infection, which were more common in the ASD group, did not affect the severity of autism, but it was shown that although the boy gender was higher in the ASD group, severely autistic children were higher in girl gender. There are differences between male and female genders in behavioral symptoms of autism. Girls have more social problems and are less able to perform the social play and social imitative play than boys. Findings about communication patterns are also discrepant. Girls have less expressive and advanced receptive language skills than boys (18,28). Thus, although the boy gender was higher in the ASD group, severely autistic children were higher in the girl gender in the present study.

Our findings should be understood in the context of some limitations. In the questionnaire form, the question about which cities of Turkey the participants live in was not available. For this reason, the results may not be generalizable to Turkey. The use of an online, cross-sectional survey is limited in its ability to determine a true cause-and-effect relationship. The data analysis was based on self-reporting data which could have an impact on the outcome of the study.

5. Conclusions

The findings of this study provide results that could be beneficial for elucidating etiology or for disease prevention and nursing care. Despite increasing studies in recent years, it is seen that the etiology of ASD is largely unknown and the level of evidence for many agents is insufficient for the relationships defined in the literature. The effect of various diseases and teratogens exposed during the fetal period on brain development is undeniable. It has been stated in the literature that chronic diseases, infections, and other teratogens that occur during the prenatal period may increase autism risk. In this study, supporting the literature, it was observed that the risk of autism increased in the presence of risk factors such as diabetes and infection in the prenatal period. For this reason, advanced studies should be carried out, and the mother and fetus should be followed up in the presence of diseases such as diabetes and infection in the prenatal period, and children with autism should be detected in the early period for bringing them to the optimal level. Educating nurses about prenatal diseases and raising awareness is of great importance as they provide care for both mothers and their children.

Contribution to the field

This study reveals the existence of a relationship between prenatal chronic diseases, infection, and autism spectrum disorder. This study is the first to examine the relationship between prenatal chronic diseases, infection, and autism spectrum disorder in Turkey.

Ethical Considerations

Ethics committee approval was obtained from the Noninvasive Clinic Ethical Committee of a university (30.12.2020 protocol no: 54674167-050.01.04-206) in Turkey. Before starting the answering questionnaire, consent was obtained. The study was conducted in accordance with the Declaration of Helsinki and verbal permission from the mothers who voluntarily participated in the research was obtained.

Conflict of Interest

This article did not receive any financial funds. There is no conflict of interest regarding any person and/or institution.

Yazarlık Katkısı

Fikir/Kavram: MT, EG; **Tasarım:** MT, EG; **Denetleme:** MT, EG; **Kaynak ve Fon Sağlama:** MT, EG; **Malzemeler:** MT, EG; **Veri Toplama ve/veya İşleme:** MT, EG; **Analiz/Yorum:** MT, EG; **Literatür Taraması:** MT, EG; **Makale Yazımı:** MT, EG; **Eleştirel İnceleme:** MT, EG.

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