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Evaluation of Prenatal and Perinatal Risk Factors in Autism Spectrum Disorder According to Disease Severity

Otizm Spektrum Bozukluğunda Prenatal ve Perinatal Risk Faktörlerinin Hastalık Şiddetine Göre Değerlendirilmesi

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ABSTRACT

Aim: This study was conducted to investigate prenatal and perinatal characteristics among the risk factors in Autism Spectrum Disorder (ASD) according to disease severity.

Materials and Methods: One hundred twenty-eight children in the ASD group and 100 children in the control group were included in the study. Prenatal and perinatal characteristics of the ASD and control groups were retrospectively evaluated using the Socio-demographic and Research Data Form. The ASD group was divided into two groups, mild-moderate ASD and severe ASD, according to the Childhood Autism Rating Scale scores.

Results: Paternal age and history of hypoxia/asphyxia during pregnancy were found to be statistically significantly higher in the severe ASD group compared to both the mild-moderate ASD group and the control group. The rate of paternal smoking during pregnancy, preterm labor, and difficult delivery history were statistically higher in both ASD groups compared to the control group.

Conclusion: This study shows that prenatal and perinatal factors are more prevalent in individuals diagnosed with ASD compared to the control group. It also found that the presence of certain factors, such as paternal age and history of hypoxia/asphyxia, was associated with more severe ASD symptoms. Our findings suggest that the identification and management of potential risk factors in the prenatal and perinatal periods may influence the severity of the disease in ASD.

Keywords: Autism spectrum disorder, prenatal, perinatal

ÖZ

Amaç: Bu çalışma, otizm spencer bozukluğu (OSB) risk faktörleri arasında yer alan prenatal ve perinatal özelliklerin hastalık şiddetine göre araştırılması amacıyla yapılmıştır.

Gereç ve Yöntem: OSB grubunda 128 çocuk, kontrol grubunda ise 100 çocuk araştırmaya dahil edilmiştir. OSB ve kontrol grubunun prenatal ve perinatal özellikleri retrospektif olarak Sosyo-demografik ve Araştırma Veri Formu kullanılarak değerlendirilmiştir. OSB grubu Çocukluk Otizmi Derecelendirme Ölçeği pualarına göre hafif-orta OSB ve şiddetli OSB olarak iki gruba ayrılmıştır.

Bulgular: Annenin gebeliğindeki baba yaşı ve hipoksi/asfiksi öyküsü şiddetli OSB grubunda hem hafif-orta OSB grubu hem de kontrol grubuna göre istatistiksel olarak anlamlı şekilde yüksek bulunmuştur. Gebelikte babanın sigara kullanımı, preterm doğum ve zor doğum öyküsü her iki OSB grubunda kontrol grubuna göre istatistiksel olarak daha yüksek bulunmuştur.

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Sonuç: Bu araştırma, prenatal ve perinatal faktörlerin OSB tanısı almış bireylerde kontrol grubuna kıyasla daha yaygın olduğunu göstermektedir. Hipoksi, asfiksi ve baba yaşı gibi belirli faktörlerin varlığının, OSB semptomlarının daha şiddetli görülmesiyle ilişkili olduğu bulunmuştur. Bulgularımız prenatal ve perinatal dönemlerdeki olası risk faktörlerinin tanımlanması ve yönetilmesinin, OSB'deki hastalık şiddetini etkileyebileceğini göstermektedir.

Anahtar Kelimeler: Otizm spektrum bozukluğu, prenatal, perinatal

INTRODUCTION

Autism Spectrum Disorder (ASD) is a serious neurodevelopmental state defined by characteristics such as difficulties in social interaction and communication, recurrent behaviors and limited fields of interest[1]. According to estimates made by the Disease Control and Prevention Centers, one in every 44 children is diagnozed by ASD[2]. The recent meta-analyses have determined the global prevalence of ASD as 0.6%, which makes it an important public health issue[3]. It creates great emotional and economic burdens on individuals, families and societies since ASD begins in early childhood age, it is lifelong disorder and it is associated with important disabilities[4,5]. Therefore, defining genetic and environmental factors that contribute to the pathogenesis of ASD is critical for understanding and managing this complex situation.

The current literature reveals that the etiology of autism cannot be fully illuminated; the general view is that this is a brain development disorder that occurs with the interaction of multiple factors[6]. Studies have emphasized on structural and functional changes in the brain, the age of the onset of these changes, and the role of genetic and environmental factors[7,8]. Environmental risk factors in the etiology of autism are often defined as factors that can affect the pre-pregnancy, which is the early period for brain development, time of birth and postnatal periods. The effects of these factors on brain development are linked to a number of processes associated with neurobiological changes[9].

In the early stages of development, both genetic and environmental factors play a vital role in the etiology of ASD[10]. The previous studies investigating prenatal and perinatal factors in the ethiology of ASD have demonstrated controversial results. In a meta-analysis, Gardener et al.[11] found that, among factors over 50, vaginal bleeding, birth damage, low birth weight, hyperbilirubinemia, pregnancy diabetes, drug exposure, advanced parent age and being the first child were associated with the risk of autism[12]. In the literature, there is not enough evidence to imply a single prenatal and perinatal factor in ASD etiology. Guinchat et al.[13] stated that there was not enough research on the effects and consequences of some risk factors.

Although it has been shown in many studies that prenatal and perinatal factors increase the risk of ASD, it is not known how these factors affect the severity of the disease. In the prenatal and perinatal process, individuals with typical autism have experienced more complications than individuals having atypical autism with less symptom severity, or those with Asperger syndrome, which shows that these factors have a potential effect on disease severity[14]. Many genetic and environmental factors that contribute to the pathogenesis of ASD lead to great variability among individuals at clinical level[15]. In a study of Wallace et al.[16], in which they examined the relationship between birth complications and ASD symptoms, they found that hypertension, preeclampsia and common edema were associated with a higher level of communication and hypertension, albuminuria and common edema were associated with more severe recurrent behaviors.

In this study, it is aimed to investigate prenatal and perinatal features, which are among the risk factors associated with ASD, according to the intensity of the disease. It is assumed that prenatal and perinatal factors may be associated with the severity of ASD symptoms. Changeable risk factors that differ depending on the severity of the disease may expand the information in this field and guide for future interventions.

MATERIALS AND METHODS

In the study, the recorded data of ASD patients aged 2-17 years, who were diagnozed in Child and Adolescent Psychiatry Outpatient Clinic at Atatürk University Faculty of Medicine and individuals who visited the outpatient clinic but was not diagnosed with any disease as a result of a psychiatric evaluation were examined retrospectively. The study included 128 children in the ASD group and 100 children in the control group.

The ASD group consisted of cases that were diagnosed with ASD according to the Criteria of DSM-5 as a result of the psychiatric evaluation. The inclusion criteria included having sufficient prenatal and perinatal data in their files for the ASD group and having Childhood Autism Rating Scale (CARS) scores. The ASD group was grouped into two as mild-moderate ASD and severe ASD, considering the CARS scores.

In the ASD group, those with genetic and neurological illnesses and those with missing file data and CARS scores were excluded from the study. In the control group, those who applied to the outpatient clinic but was not diagnozed with any psychiatric disease according to DSM-5 criteria and those

whose prenatal and perinatal data were sufficient in their files met the criteria for the study. Moreover, in the control group, those with psychiatric illness according to the DSM-5 criteria, neurological and genetic disease, and those who had missing file information were excluded from the study.

The research was carried out by taking the necessary permissions from the Ethics Committee of the Clinical Research, Atatürk University Faculty of Medicine, (decision no: B.30.2.01.00/05, date: 21.02.2024).

Measurement Tools

Sociodemographic and Research Data Form

Sociodemographic information of the ASD and the control groups were evaluated using the sociodemographic and Research Data Form developed by the authors. Parent age during pregnancy, father age in the mother's pregnancy, parent age difference, medical illness of the mother, psychiatric illness of the mother, history of trauma in pregnancy, threatened abortion, infection in pregnancy, the use of any medication by the mother in pregnancy, alcohol consumption or smoking habit of the mother in pregnancy, and smoking habit of the father during mother's pregnancy are the prenatal features evaluated in the research. Delivery method, delivery time, history of dystocia, history of hypoxia-asphyxia, history of incubator and intensive care, and the story of newborn jaundice constitute the perinatal features examined in the research.

Childhood Autism Rating Scale

This behavioral rating scale developed by Schopler et al.[17] 1980 is used to distinguish children who show and do not show the signs of autism. This scale, which is used internationally in the diagnosis and screening of autism, is a reliable and valid assessment tool that can rate the severity of autism as mild, moderate and severe. The scale consisting of 15 items rates behaviors from 1 to 4, the minimum score is 15 and the maximum score is 60. Autism severity is rated according to the score intervals. Its Turkish adaptation was made by Gassaloğlu et al.[18] 2016.

Hollingshead-Redlich Scale

The Hollingshead-Redlich scale was used in this study to determine the socioeconomic and socio-cultural levels of families. This scale classifies the socioeconomic status of the family with a general evaluation based on the professional status and education levels of the parents[19]. Within the scope of the research, the socioeconomic and socio-cultural levels of the participating families were filled in a way that reflected the highest reached level determined by the researchers.

Statistical Analysis

Data were evaluated in IBM SPSS Statistics 27.0 (IBM Corp., Armonk, New York, USA) Statistics Package Program. The descriptive statistics were given as unit number, percentage, mean ± standard deviation, median (Q_1-Q_3) values. With the Fisher's exact test, it was investigated whether there was a difference between the groups in terms of frequency. The normal distribution of data of numerical variables was evaluated with the Shapiro Wilk normality test and Q-Q graphics. The comparisons between the groups were performed with ANOVA analysis for normally distributed variables and with Kruskal-Wallis analysis for non-normally distributed variables. As a multiple comparison test, Tukey HSD was used for normally distributed variables and the Dunn-Bonferroni test was used for non-normally distributed variables. The value of $p<0.05$ was considered statistically significant.

RESULTS

In the study, there was no statistically significant difference between the groups in terms of age, gender and the socioeconomic-sociocultural level of parents. Sociodemographic features are presented in Table 1. Of the prenatal features, the age of the father at the mother's pregnancy was found to be statistically significantly higher in the severe ASD group than both in the mild-moderate ADS group and in the control group ($p=0.039$). During pregnancy, the father's smoking rate was found to be statistically higher in both ASD groups than in the control group ($p=0.008$). The prenatal features of the groups are presented in Table 2. Of the prenatal features, preterm birth and history of dystocia were found to be statistically significantly higher in the ASD groups compared to the control group ($p=0.018$, $p<0.001$). Story of hypoxia/asphyxia was statistically significantly higher in the severe ASD group compared to the mild-moderate ASD group and control group ($p=0.025$). The perinatal features of the groups are presented in Table 3.

DISCUSSION

In this study, the relationship between prenatal and perinatal characteristics considered as risk factors associated with ASD and the severity of the disease was examined. Our study showed that the father's age at the mother's pregnancy was significantly higher in the severe ASD group compared to both the mild-moderate ASD group and the control group. During pregnancy, the father's smoking rate was significantly higher in both ASD groups than in the control group. Of the perinatal features, preterm birth and history of dystocia were significantly higher in the ASD groups compared to the control group, and the story of the hypoxia/asphyxia was significantly higher in the severe ASD group than in other groups.

Risk factors can be defined as measurable properties that increase the sensitivity of an individual to a particular health issue. Various risk factors combine with possible biological mechanisms that may lead to ASD in the prenatal or perinatal period[20,21]. These risk factors, which are important in terms of early diagnosis and intervention, can help to detect groups or individuals at risk before symptoms become clear. In addition, for individuals who are suspected of having ASD or who have received this diagnosis, mentioned factors may provide reasonable explanations about the possible causes of the disease[22]. Risk factors that have been detected in our study, which vary according to the severity of the disease, may guide

Table 1. Sociodemographic characteristics of the groups

	Mild-moderate ASD (n=80)	Severe ASD (n=48)	Control (n=100)	p-value
Age, median (Q_1-Q_3)	5 (3.25-9.50)	6 (4.00-12.00)	5 (3.00-8.00)	0.402
Gender, %, n				
Male	85.0% (68)	81.3% (39)	76% (76)	0.313
Female	15.0% (12)	18.8% (9)	24% (24)	
Socioeconomical-socia-cultura levels of parents				
Parents with university degree, having a profession, or working at a high administrative position	50% (40)	35.4% (17)	54% (54)	0.079
Small businessman, civil servant or skilled worker, high school graduate parents	36.3% (29)	31.3% (15)	30% (30)	
Parents who are semi-skilled workers, having educational level below high school	13.8% (11)	31.3% (15)	14% (14)	
Parents who are semi-skilled workers, without any educational degree, at the education level of primary school	0% (0)	2.1% (1)	2% (2)	

ASD: Autism Spectrum Disorder, n: Number, Q_1-Q_3: Median

Table 2. Prenatal features of the groups

	Mild-moderate ASD (n=80)	Severe ASD (n=48)	Control (n=100)	p-value
Mother's age at pregnancy, median (Q_1-Q_3)	27.50 (24-31)	28.00 (25-32)	27.00 (24-31)	0.475
Father's age at mother's pregnancy, (SD)	32.12 (5.70)[ab]	33.54 (5.80)[a]	31.07 (5.26)[b]	0.039
Difference between mother and father, year, median (Q1-Q3)	5.00 (1-7)	4.00 (2-6)	3.00 (1-6)	0.111
Mother's medical disease %, (n)	14 (17.5%)	11 (22.9%)	12 (12%)	0.229
Mother's psychiatric disease %, (n)	8 (10%)	2 (4.2%)	3 (3%)	0.124
History of trauma at pregnancy %, (n)	4 (5%)	1 (2.1%)	2 (2%)	0.267
Threatened abortion %, (n)	17 (21.3%)	8 (16.7%)	18 (18%)	0.920
Having infection during pregnancy %, (n)	17 (21.3%)	5 (10.4%)	9 (9%)	0.052
Mother's using a medication during pregnancy %, (n)	24 (30%)	16 (33.3%)	19 (19%)	0.103
Mother's using alcohol / smoking during pregnancy, %, (n)	4 (5%)	2 (4.2%)	10 (10%)	0.315
Father's smoking during mother's pregnancy, %, (n)	52 (65%)[a]	32 (66.7%)[a]	45 (45%)[b]	0.008

The superscripts[a, b] show difference between the groups. There is no difference in the groups with the same letters. ASD: Autism Spectrum Disorder, SD: Standard deviation, n: Number, Q_1-Q_3: Median

Table 3. Perinatal features of the groups

	Mild-moderate ASD (n=80)	Severe ASD (n=48)	Control (n=100)	p-value
Cesarean birth, %, (n)	39 (48.8%)	27 (56.3%)	41 (41%)	0.222
Preterm birth, %, (n)	23 (28.7%)[a]	15 (31.3%)[a]	14 (14.3%)[b]	0.018
Dystocia, %, (n)	18 (22.5%)[a]	9 (18%)[a]	4 (4%)[b]	<0.001
Hypoxia-asphyxia, %, (n)	10 (12.5%)[ab]	8 (16.7%)[a]	4 (4%)[b]	0.025
Incubator-intensive care, %, (n)	18 (22.5%)	10 (20.8%)	10 (10%)	0.057
Newborn jaundice, %, (n)	11 (13.8%)	7 (14.6%)	5 (5%)	0.088

The superscripts[a, b] show difference between the groups. There is no difference in the groups with the same letters. ASD: Autism Spectrum Disorder, n: Number

clinicians to predict the clinical course of children under the risk of ASD or who are diagnosed with ASD. These findings suggest that recognition and management of risk factors can play a critical role in early diagnosis and intervention of ASD. For this reason, a detailed examination of risk factors for prenatal and perinatal periods is of great importance in terms of developing strategies for the prevention and management of ASD.

Research assessing ADS risk factors have reported that parent age may be a risk factor[23]. Studies have shown that children born from older parents have a higher risk of development of ASD. In particular, the advanced age of father is thought to increase the risk of ASD by increasing the nova mutation and epigenetic change rates. The relationship between advanced mother's age and the risk of ASD is explained with more frequent development of pregnancy and birth complications[23]. The findings of our study reveal that the advanced age of father is an important factor for the risk of ASD in accordance with the tendencies specified in the literature. On the other hand, there was no relationship between advanced mother's age and ASD in our study. This suggests that the potential relationship between the mother's age and the risk of ASD is more complex and perhaps other intermediate variables may play a role in this relationship. The impact of the advanced age of father on the risk of ASD may be a factor that should be considered in genetic counseling and planned pregnancies.

Smoking is considered a potential risk factor for ASD due to its biologically harmful effects and high prevalence. In two separate meta-analysis studies on the effect of the mother's smoking status on the risk of ASD in children in the prenatal period, no definite evidence of this relationship could be obtained[24,25]. However, based on a large epidemiological sampling, a recent study evaluating the effects of fathers' prenatal smoking status on the risk of ASD showed that the father's smoking in the prenatal period significantly increased the likelihood of ASD in children[26]. In parallel to the literature, our research also revealed that the father's prenatal smoking rates were higher compared to the healthy control group, but there was no evident difference in the prenatal smoking stutus of the mother. These findings suggest that there may be a complex relationship between parents' smoking status and ASD. The obtained results indicate that the fact that families avoid smoking during pregnancy planning and process may reduce the risk of ASD in children.

Various risk factors specific to the perinatal period lead to neurobiological fragility, increasing the risk of ASD and other neurodevelopmental conditions. Some of the perinatal factors that increase the risk of ASD are birth trauma, low 5-minute APGAR score and cesarean delivery, low birth weight (<2500 g), and umbilical cord complications[12]. These risk factors cause inflammation in the nervous system, irregularity of signal paths and neural damage[20]. In our study, preterm birth and history of dystocia were observed to be significantly higher in groups diagnosed with ASD compared to the control group. In a study conducted on children with ASD in Türkiye, preterm birth and dystocia were found to be among the important risk factors[27]. Improvements in health services, especially in the monitoring of pregnancy, can reduce the effects of preventable risk factors encountered in prenatal and perinatal periods on the development of ASD.

Hypoxia/asphyxia story can cause serious health problems in newborn infants and may contain both mother and baby-specific factors. Umbilic cord problems, placenta problems, long or difficult births, maternal problems, prenatal complications, fetal anomaly, premature birth, and environmental factors that the mother is exposed to can increase the risk of hypoxia/asphyxia[28-30]. In our study, it was found that hypoxia/asphyxia history was significantly higher in the group with severe ASD compared to both the mild-moderate ASD group and the control group. A recent study has shown that prenatal and perinatal risk factors, which lead to a history of hypoxia/asphyxia in children with ASD, are associated with the severity of ASD symptoms[31]. Current research and our findings indicate that prenatal and perinatal characteristics may potentially affect ASD severity. The effects of these features on early neurodevelopment and how they lead to severe symptoms in later periods are issue of concern for advanced research and detailed studies are required in this field.

Newborn jaundice, which requires intensive care among the perinatal factors, is a remarkable factor in terms of ASD risk[32]. However, in the studies conducted, the relationship between newborn jaundice and ASD symptom severity could not be found[6,31]. Although the story of incubator-intensive care and newborn jaundice is not statistically significant among the groups, high rates close to the significance level in the ASD group are remarkable. These findings emphasize the importance of future research by using large samples to better understand the role of these special situations in the perinatal period in ASD development.

The results of this study should be interpreted carefully. In particular, the data on the prenatal and perinatal events reported by parents may be misleading due to the accuracy of recall that may be disrupted by subjectivity and the transition of time. This may lead to misleading or incomplete information about mothers' medical conditions and complications during birth, which can potentially affect the accuracy of research findings[33].

Study Limitations

In our study, some obstetric complications (polyhydramnios, oligoamnios, placenta previa, umbilical cord knot) could not be examined because they were rare for group comparisons. Instead, the effects of these situations on ASD risk were evaluated by focusing on general characteristics such as history of dystocia and hypoxia/asphyxia. A larger cohort is required to determine the difference in small effect. Therefore, it is important for future research to deal with these limitations and to verify these pre-findings using wider sample groups. The lack of use of structured evaluation tools when creating the ASD group is among the limitations. The similar sociodemographic features of the groups and the evaluation of risk factors according to the severity of the disease are among the strong aspects of our research. The fact that the studies examining prenatal and perinatal characteristics in individuals with ASD according to the severity of the disease are limited shows that this study fills the information gap in the field. Our study contributes to the understanding of the etiology and severity of ASD and offers valuable insights on the possible causes of the disease. In this context, comprehensive and multidisciplinary research is needed to better understand the complex nature of ASD and the various factors affecting it.

CONCLUSION

This study shows that prenatal and perinatal factors are more common in individuals who are diagnosed with ASD than the healthy control group. The study has found that the presence of certain factors is related to the more severe observation of ASD symptoms. The findings provide significant evidence that these early factors may affect the clinical occurrence of the ASD. This shows that identification and management of risk factors in prenatal and perinatal periods may have the potential to reduce the effects of ASD. Therefore, future research should examine these relationships in more detail and determine how this information can be used in developing strategies for the prevention and management of ASD.

Ethics

Ethics Committee Approval: The research was carried out by taking the necessary permissions from the Ethics Committee of the Clinical Research, Atatürk University Faculty of Medicine, (decision no: B.30.2.01.00/05, date: 21.02.2024).

Informed Consent: Prenatal and perinatal characteristics of the ASD and control groups were retrospectively evaluated using the socio-demographic and Research Data Form.

Footnotes

Authorship Contributions

Concept: A.B., H.İ., E.Y.D., Design: A.B., E.Y.D., M.A.A., S.B., Data Collection or Processing: H.İ., K.B., E.Y.D., S.B., Analysis or Interpretation: A.B., H.İ., E.Y.D., S.B., Literature Search: A.B., H.İ., K.B., Writing: A.B., H.İ., K.B., E.Y.D., M.A.A., S.B.

Footnotes

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