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Exploration of Risk Factors for Language Regression According to Parent Reports in Turkish Children with Autism Spectrum Disorder

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ABSTRACT

Background: Approximately 30% of autism spectrum disorder (ASD) cases exhibit developmental regression after a period of typical development, leading to what is known as regressive autism. Our understanding of the factors underlying regression, including precise mechanisms, clinical features, and risk factors, remains limited. This study aims to compare children with ASD with language regression (ASD-LR) to those without developmental regression (ASD-NR) in terms of clinical and demographic characteristics and to identify potential predictors.

Methods: In this cross-sectional retrospective study, children aged 2-6 diagnosed with ASD-LR were matched for age and gender with children diagnosed with ASD-NR between January 2023 and January 2024. The groups were compared in terms of demographic and clinical characteristics.

Results: The mean age of the ASD-LR group (n = 32) was 52.16 ± 14.56 months, and the ASD-NR group (n = 50) had a mean age of 48.76 ± 13.41 months. Univariate analyses revealed no significant differences in autism severity between groups in clinician ($P = .367$) and parent evaluations ($P = .541$). However, in the ASD-LR group, a significant relationship was found between regression, a history of febrile seizures ($P = .012$), a father's psychiatric background ($P = .002$), and a family history of psychiatric disorders ($P < .001$). Family history of psychiatric disorders (OR 7.54, 95% CI 1.10-51.64, $P = .040$) and cesarean delivery (odds ratio 3.90, 95% CI 1.05-14.47, $P = .042$) were identified as independent predictors of language regression.

Conclusion: The results indicate that regression may be associated with both genetic and environmental factors, including a family history of psychiatric disorders, cesarean delivery, and febrile seizure. Future research should focus on explaining these factors and identifying potential preventive measures.

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by challenges in social communication and interaction, along with dysfunctional restricted interests and repetitive behaviors.[1] Recent data indicate an increasing prevalence of ASD, with an incidence of 1 in 36 among children in the United States.[2] While the cause of autism is heavily influenced by genetic factors, numerous perinatal risk factors have been identified in previous studies.[3,4]

Parents often report atypical symptoms in most patients with ASD from early infancy. Additionally, some cases describe a gradual or sudden loss of acquired speech and/or social interaction skills.[5] In the phenomenon known as autistic regression, declines are primarily observed in language skills, but they may also manifest in other areas of functionality, such as eye contact, imitation-based games, joint attention, and gestural communication.[6] Developmental regression is not a specific symptom of ASD;[7] however, studies indicate that it is more frequently experienced in groups with ASD compared to those without.[6] A meta-analysis study reported that ASD with regression was observed in 32% of children with ASD occurring at a mean age of 19.8 months.[8] Lost skills are regained within months or years in some cases, while the loss may be permanent in others.[9]

Studies comparing ASD with regression to those without developmental regression (ASD-NR) in terms of clinical characteristics indicate that symptoms are more severe in ASD with regression,[6] with lower cognitive abilities, ten more prevalent receptive and expressive language

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disorders, and sleep disorders.[11] Some studies have reported a higher frequency of epileptiform anomalies in ASD with regression.[12] However, contrary to these findings, there are also studies suggesting no significant differences in clinical features between ASD with regression and ASD-NR.[13,14] One of the primary reasons for these discrepancies among studies is the lack of a common definition for regression and the utilization of different measurement tools.[7]

Non-regressive autism spectrum disorder - is associated with various genetic factors,[15] and perinatal risks such as gestational hypertension/placenta previa,[6] immunological factors,[16] neurological factors,[17] and gastrointestinal abnormalities.[18] Families of children with ASD with regression are more likely to exhibit autoimmune symptoms than those with ASD-NR and are more prone to neuropsychiatric diseases.[19] Additionally, cultural differences play a role in reporting regression; African American parents are more likely than Hispanic parents to describe regression, and Hispanics report regression more frequently than European parents.[20]

The genetic or pathophysiological processes underlying regression have not yet been elucidated, and there are significant information gaps in the literature regarding the course and outcomes of regression.[15] Understanding the intricacies of developmental regression in children with ASD is crucial for tailoring effective interventions and support strategies. Language regression, especially within the context of ASD, is a widely acknowledged phenomenon that is not typically observed in other forms of developmental delays.[21] The primary aim of our study is to compare a group consisting of autism spectrum disorder with language regression (ASD-LR) and ASD-NR in terms of clinical and demographic characteristics and to examine the relationship between language loss, perinatal risk factors, and family history. A limited number of studies have been conducted on autistic regression in Türkiye.[22] This study aims to contribute to this knowledge gap by examining potential predictors and correlates of language regression in Turkish children.

MAIN POINTS

- Groups with and without a history of language regression shows similar levels of autism severity based on parental and clinician assessments.
- In the context of regressive autism, there is a higher prevalence of febrile seizures and a family history of psychiatric disorders.
- Cesarean delivery and a family history of psychiatric disorders are predictors of regression.
- Environmental risk factors, not only genetic ones, also play a role in regression.
- There is a need for further clarification of regressive autism terminology and exploration of the interaction between genetic susceptibilities and environmental influences within the context of regressive autism.

MATERIAL AND METHODS

Participants

The data for this retrospective cross-sectional study were collected at Ankara Etlik City Hospital between February 15 and February 22, 2024. Ethics committee approval from the Ankara Etlik City Hospital was obtained (Date: February 14, 2024; Protocol number: 2024/155). Informed consent was obtained from the parents of all children, following the principles of the Declaration of Helsinki. The research participants were selected from children who attended the hospital's Child and Adolescent Mental Health outpatient clinic last year (between January 2023 and January 2024) and were diagnosed with ASD according to the diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5). Confirmation of the diagnosis was obtained from at least 2 child and adolescent psychiatrists who had completed their residency training.

In this study, language regression is defined as the child's failure to spontaneously use at least 3 meaningful words for at least 1 month, excluding "mother" and "father," despite having used these words continuously for at least 1 month before reaching 36 months of age, as reported by parents.[23] The inclusion criteria were parents living in Türkiye who were literate in Turkish, along with their children diagnosed with ASD. For ASD-LR, exclusion criteria included the presence of regression in functional areas beyond language and regression associated with organic causes such as trauma or encephalopathy. The presence of chronic diseases other than epilepsy (diabetes, celiac disease, organ failure, cancer, etc.) or genetic conditions (Down syndrome, fragile X, Rett syndrome, etc.) in the child was considered an exclusion criterion for both groups. Out of the 268 children aged 2-6 diagnosed with ASD and followed up at the clinic in the last year, parents of 52 cases with a history of language loss were contacted by phone. Parents and their children (n = 32) who met the research criteria and agreed to participate in the study were invited for an interview and subsequently included in the ASD-LR group. Fifty age- and gender-matched children diagnosed with ASD who applied within the same date range and had no history of developmental regression were included in the ASD-NR group. During the interview, the child's ASD diagnosis was re-evaluated by the researcher according to DSM-5 criteria. Parents completed the sociodemographic data form and the Autism Behavior Checklist (ABC); the child psychiatrist filled out the Childhood Autism Rating Scale (CARS).

Measures

Sociodemographic Data Form: The survey was developed by researchers to gather diverse sociodemographic information and clinical characteristics of children with ASD and their parents. It included inquiries about gender,

age, number of siblings, history of febrile convulsions and epilepsy, perinatal risk factors, developmental stages, and family history of psychiatric disorders.

Childhood Autism Rating Scale: It is a behavioral rating scale consisting of 15 items, developed to differentiate between children with intellectual disabilities (ID) and those with ASD. The CARS allows for the determination of the clinical severity of autism, classified as mild, moderate, or severe. Each item is rated on a scale of 1-4, with the option of a half-point rating.[24] The total score can range from a minimum of 15 to a maximum of 60. According to the scoring: children with scores between 15 and 29.5 are not considered to have autism; those scoring 30-36.5 are clinically regarded as having mild to moderate autism; and those with scores of 37-60 are regarded as severe autism. The Turkish validity and reliability study of the scale was conducted by Sucuoğlu et al.[25]

Autism Behavior Checklist: It is a 57-item assessment tool used for screening and differential diagnosis of autism. It comprises 5 subscales: sensory domain, relationship building, body and object use, language skills, and social and self-care skills. The scale ranges from a minimum score of 0 to a maximum score of 159.[26] The Turkish adaptation of the scale has been validated and proven reliable.[27]

Statistical Analysis

Data analysis was conducted using (Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM SPSS Corp., Armonk, NY, USA). Skewness-kurtosis values and Kolmogorov-Smirnov test were examined for the distribution of the data. After descriptive analyses, groups were compared using the Pearson chi-square test (χ^2) or Fisher exact test (when chi-square test assumptions do not hold due to low expected counts) for categorical variables and the Student's *t*-test for continuous variables. Binary logistic regression analysis was applied to identify predictors of language regression. Regression was considered dependent in this analysis, and variables with $P < .1$ in univariate analyses were taken as independent variables. The "Enter" method was used for regression. Logistic regression assumptions were tested before the analysis, including correlation coefficients, variance inflation factor (VIF), tolerance values, and Cook's distance. The goodness-of-fit of the regression model was evaluated with the Hosmer-Lemeshow goodness-of-fit statistics. A significance level of $P < .05$ was considered for all analyses.

RESULTS

The mean age of the ASD-LR group (n = 32) included in the study was 52.16 ± 14.56 months, with 4 (12.5%) females and 28 (87.5%) males. The ASD-NR group (n = 50) had a mean age of 48.76 ± 13.41 months, with 5 (10%) females and 45 (90%) males. In the ASD-LR group, language loss started on the mean at 19.4 months. The ASD-LR group's CARS score was a mean of 37.86 ± 6.14, and the ABC score was a mean of 56.16 ± 22.45. These values were calculated as 36.45 ± 7.86 and 52.96 ± 23.38, respectively, in the ASD-NR group. There was no statistically significant difference between the groups in terms of CARS [t (76.7) = −0.91, $P = .367$] and ABC [t (80) = −0.61, $P = .541$] score means. Fisher's exact test did not indicate a significant association between language regression and epilepsy ($P = .524$); however, a significant association was found with a history of febrile convulsions ($P = .012$).

The mean age of mothers in the ASD-LR group was 31.81 ± 6.27 years, and for fathers, it was 35.78 ± 7.95 years, with most of the parents (n = 32, 50%) having a university degree. Similarly, in the ASD-NR group, the mean age of mothers was 31.27 ± 5.30 years, and for fathers, it was 34.52 ± 5.23 years, with most of the parents (n = 39, 39%) being university graduates. In the ASD-LR group, 6 (18.8%) of mothers and 8 (25%) of fathers had a known diagnosis of affective disorder, while in the ASD-NR group, this was observed in 4 (8%) of mothers and 1 (2%) of fathers. Among the children in the ASD-LR group, 12 (37.5%) had a family history of psychiatric disorder in second-, third-, or fourth-degree relatives (affective disorders (n = 7), neurodevelopmental disorders (n = 4), psychotic disorder (n = 1)); this rate was 4% (n = 2) in the ASD-NR group (affective disorders (n = 1), neurodevelopmental disorders (n = 1)). While the relationship between maternal psychiatric disorder and language regression was not significant in the chi-square test ($P = .177$), a significant association was found between paternal psychiatric disorder ($P = .002$) and familial psychiatric disorder ($P < .001$) with regression. The findings of the analyses comparing the groups in terms of clinical, sociodemographic characteristics, and family history are presented in Table 1.

Subsequently, the groups were compared based on parental reports for perinatal risk factors such as the threat of miscarriage, alcohol and cigarette use during pregnancy, maternal stress, medication usage, infection history during pregnancy, parents' ages at childbirth, mode of delivery, gestational age, postnatal hypoxia, icterus, meconium aspiration, blood incompatibility, postnatal respiratory infection, and other factors. No significant difference was found between the groups regarding perinatal risk factors (Table 2).

Finally, a logistic regression model was constructed using variables with $P < .1$ in univariate analyses (presence of paternal psychiatric disorder, presence of familial psychiatric disorder, mode of delivery, and presence of febrile convulsions) to identify factors predicting language regression. Before the analysis, it was observed that the correlation coefficients between the variables were less than 0.9,[28] no multicollinearity issues (VIF < 5, tolerance > 0.2),[29] and there were no outliers (Cook distance < 1.0).[30]

Table 1. Comparison of the Groups in Terms of Sociodemographic and Clinical Characteristics

Parameters	ASD-LR (n=32) M (±SD)/n (%)	ASD-NR (n=50) M (±SD)/n (%)	*P*
Children with ASD			
Age (month)	52.16 (±14.56)	48.76 (±13.41)	.282[a]
Sex			
Female	4 (12.5%)	5 (10%)	.731[c]
Male	28 (87.5%)	45 (90%)	
Age at diagnosis (month)	34.16 (±10.58)	32.92 (±9.99)	.596[a]
Febrile convulsion	8 (25%)	2 (4%)	**.012**[c*]
Comorbid epilepsy	6 (18.8%)	6 (12%)	.524[c]
CARS score	37.86 (±6.14)	36.45 (±7.86)	.367[a]
ABC score	56.16 (±22.45)	52.96 (±23.38)	.541[a]
Parents' marital status			
Married	31 (96.9%)	49 (98.0%)	.631[c]
Divorced/separated	1 (3.1%)	1 (2%)	
Number of siblings			
0	11 (34.4%)	18 (36.0%)	.516[b]
1	15 (46.9%)	27 (54.0%)	
≥2	6 (18.8%)	5 (10.0%)	
Mothers			
Age (years)	31.81 (±6.27)	31.27 (±5.30)	.675[a]
Education status			
Primary	4 (12.5%)	8 (16%)	.276[b]
Secondary	8 (25.0%)	6 (12%)	
High	6 (18.7%)	17 (34%)	
College	14 (43.8%)	19 (38%)	
Working status			
Working	13 (40.6%)	13 (26.0%)	.165[b]
Not working	19 (59.4%)	37 (74.0%)	
Psychiatric background (yes)	6 (18.8 %)	4 (8 %)	.177[b]
Fathers			
Age (years)	35.78 (±7.95)	34.52 (±5.23)	.431[a]
Education status			
Primary	7 (21.9%)	7 (14%)	.909[b]
Secondary	3 (9.4%)	3 (6%)	
High	4 (12.5%)	20 (40%)	
Collage	18 (56.2%)	20 (40%)	
Working status			
Working	31 (96.9%)	50 (100%)	.390[c]
Not working	1 (3.1%)	0	
Psychiatric background (yes)	8 (25%)	1 (2%)	**.002**[c*]
Family history of psychiatric disorders			
Yes	12 (37.5%)	2 (4%)	**<.001**[b*]
No	20 (62.5%)	48 (96%)	

ASD-LR, autism spectrum disorder with language regression; ASD-NR, autism spectrum disorder without developmental regression; ABC, Autism behavior checklist; CARS, Childhood Autism Rating Scale; M, mean; SD, standard derivation.
[a]Student *t*-test.
[b]Pearson χ^2 test.
[c]Fisher's exact test.
*$P < .05$.

Table 2. Univariate Analyses of Perinatal Risk Factors

Variables	ASD-LR (n=32) M (±SD)/n (%)	ASD-NR (n=50) M (±SD)/n (%)	*P*
Maternal age at delivery (years)	27.47 (±6.78)	27.21 (±5.57)	.851[a]
Paternal age at delivery (years)	31.43 (±8.32)	30.46 (±5.48)	.559[a]
Threatened miscarriage (yes)	11 (34.4%)	12 (24%)	
Prenatal risk (yes)	17 (40%)	20 (53.1%)	.244[b]
Smoking during pregnancy	6 (18.8)	7 (14%)	
Alcohol consumption	-	-	
Stress	8 (25%)	9 (18%)	
Infection	4 (12.5%)	5 (10%)	
Drug use	5 (15.6%)	7 (14%)	
Mode of delivery			
Natural delivery	7 (21.9 %)	20 (40 %)	.088[b]
Cesarean section	25 (78.1%)	30 (60 %)	
Gestational age at birth			
Preterm / Postterm (yes)	4 (12.5 %)	5 (10%)	.731[c]
Term (yes)	28 (87.5 %)	45 (90%)	
Cyanosis (yes)	0	2	.518[c]
Meconium aspiration (yes)	0	1	.390[c]
Icterus (yes)	12	16	.608[b]
Blood-incompatibility (yes)	5	2	.104[c]
Respiratory infection (yes)	0	1	.390[c]

ASD-LR, autism spectrum disorder with language regression; ASD-NR, autism spectrum disorder without developmental regression; M, mean; SD, standard deviation.
[a]Student's *t*-test.
[b]Pearson χ^2 test.
[c]Fisher's exact test.

Thus, the variables met the assumptions for logistic regression. This model explained the variance in language regression, accounting for 36.8% of the change (Nagelkerke R^2) significantly, $\chi^2 = 25.97(4)$, $P < .001$. The analysis results revealed that the presence of psychiatric disorder (odds ratio (OR) 7.54, 95% CI 1.10-51.64, $P = .040$) and cesarean delivery (OR 3.90, 95% CI 1.05-14.47, $P = .042$) were independent predictors of language regression (Table 3).

DISCUSSION

As far as we know, this research stands out as one of the rare studies evaluating risk factors for language regression in Turkish children with ASD. The findings of the study highlight a significant association, such as the more widespread occurrence of febrile convulsions and a family history of psychiatric disorders among individuals with ASD-LR. Additionally, the study reveals a previously unreported association; it demonstrates that delivery by cesarean section and a family history of psychiatric disorders independently predict language loss in children

Table 3. Multiple Logistic Regression Analysis of Factors Predicting Language Regression

	B	SD	Wald	Exp(B) (95% CI)	*P*
Constant	-2.076	.626	11.006	0.125	.001
Febrile convulsion (1 = yes)	1.797	.987	3.314	6.031 (0.871-41.746)	.069
Psychiatric disorder in father (1 = yes)	1.480	1.275	1.348	4.393 (0.361-53.443)	.246
Family history of psychiatric disorders (1 = yes)	2.020	.982	4.232	7.537 (1.100-51.637)	**.040***
Mode of delivery (1 = Cesarean section)	1.362	.668	4.153	3.904 (1.053-14.470)	**.042***

ASD-LR, autism spectrum disorder with language regression. Omnibus test: X^2 = 25.974, $P < .001$, -2 log probability = 83.719, Nagelkerke R^2 = 0.368, Hosmer and Lemeshov Test X^2 = .385, P = .825, dependent variable: language regression, no (0); yes (1).
*$P < .05$.

with ASD. This study contributes a new perspective to the heterogeneity of ASD in the context of regressive autism. In the study, parents reported regression occurring on average at 19.4 months, aligning with reports indicating that regression mainly occurs before the 24th month.[31,32] Furthermore, the findings are consistent with previous research that did not find a significant difference in the severity of autism between groups.[13,14]

While febrile convulsion history was identified more frequently in the regressive group (25%) in this study, no relationship was found between epilepsy and regression, consistent with other studies.[11,16] Zhang et al. reported that febrile convulsions were more common among children with ASD with regression compared to ASD-NR and the general population (20.6%). Febrile convulsions predicted regression, and they highlighted the temporal similarity between febrile convulsions, mostly occurring before the age of 3, with a peak in the second year of life, and autistic regression.[19] It is suggested that the observed relationship between febrile convulsions and regressive autism may reflect common genetic vulnerabilities or disruptions in early neurodevelopmental processes.[19]

In a highly participatory community-based study with a sample size of 567436, the presence of a family history of psychiatric disorders such as neurodevelopmental, affective, non-affective psychotic, obsessive-compulsive, and neurotic personality disorders, as well as neurological disorders like cerebral palsy and epilepsy among relatives (decreasing progressively in the first, second, third, and fourth degrees), was associated with an increased risk of ASD in the index individual.[33] It has been reported that this familial association is more pronounced in high-functioning autism without accompanying ID. The relationship between a family history of psychiatric disorders and an increased risk of regressive ASD may be attributed to shared common genes as well as shared environmental exposures and their interactions. Future research should investigate the molecular mechanisms underlying these connections and shed light on potential biomarkers or therapeutic targets.

While cesarean section was previously preferred in cases of complications that could jeopardize the health of the mother or the child, in recent times, it has become more commonly chosen without any indication (elective).[34] However, despite the known risks associated with a cesarean section for both the mother and the baby,[35,36] interestingly, recent meta-analyses have reported a 10%-30% increased risk of neurodevelopmental disorders such as ASD, ADHD, and ID in cesarean births compared to vaginal delivery.[37-39] The relationship between cesarean delivery and ASD is explained by various hypotheses that have been proposed. These hypotheses include the disruption of bacterial colonization in the infant,[40] abnormal immune responses,[35] and exposure to general anesthesia, which may cause neurotoxic effects on the brain.[41] Subsequent studies have reported that exposure to general anesthesia during a cesarean section, regardless of medical indication, exerts a detrimental impact on brain development, heightening the risk of ASD. Furthermore, no significant association between cesarean section and other developmental delays was observed.[42,43] In this study, it was identified that the risk of language regression was 3.9 times higher in cesarean deliveries compared to vaginal births. Nevertheless, the evaluation did not encompass considerations of whether the cesarean section was medically indicated or the type of anesthesia administered, whether local or general. Although understanding the exact mechanisms is challenging, considering the globally increasing rates of cesarean sections, further research is needed to test hypotheses regarding the role of altered microbial colonization, maternal stress, or the impact of anesthesia applications on neurodevelopment.

The findings of this study should be interpreted considering some limitations. The small sample size restricts the power to identify risk factors for ASD-LR and limits generalizability. Additionally, the retrospective design and reliance on parental reports may introduce recall bias and incomplete reporting. Furthermore, the study lacks an assessment of intelligence levels in children with ASD and focuses exclusively on language regression, representing additional limitations.

As a result, this research contributes to the literature by identifying a family history of psychiatric disorder and cesarean delivery as potential risk factors for ASD-LR, drawing attention to the heterogeneity of ASD. The findings suggest that regression in ASD may not solely arise from genetic risk factors but could also be associated with early life events. Considering this, future extensive longitudinal studies and neurobiological assessments may

provide a more detailed understanding of developmental trajectories and potential intervention points. There is a need for further clarification of regressive autism terminology and exploration of the interaction between genetic susceptibilities and environmental influences within the context of regressive autism.

Ethics Committee Approval: This study was approved by the Ethics Committee of Ankara Etlik City Hospital (Approval Number: 2024/155; Date: February 14, 2024).

Informed Consent: Informed consent was obtained from the all parents who agreed to take part in the study.

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