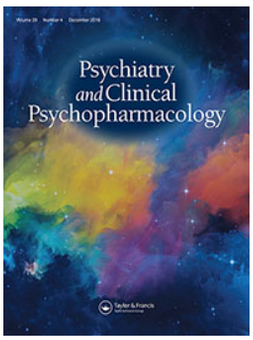

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Birth order and reproductive stoppage in families of children with autism spectrum disorder

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ABSTRACT

OBJECTIVES: The objective of the study was to evaluate the birth order of children with Autism Spectrum Disorder (ASD) and ways of delivery at birth, together with the phenomenon of reproductive stoppage and the number of siblings in the case families (families of children with ASD in the study).

METHODS: One hundred and ninety-six subjects with ASD and 54 healthy children were included into the study. Demographics were collected. Autism Behaviour Checklist (ABC), Aberrant Behaviour Checklist (AbBC), and Childhood Autism Rating Scale (CARS) were administered. Depending on the type of data and on the objective of the assessment, Mann–Whitney *U*-test, chi-square test, and Spearman tests were used for statistical analysis. A *p*-value smaller than .05 was considered to be statistically significant.

RESULTS: In the study group consisting of children with ASD, the rate of being the first-born child was determined to be more frequent, significantly, compared to the rate in the control group ($p = .001$). It was also found that 86.7% ($n = 170$) of the children in the ASD group had at least one sibling compared to the rate of 81.5% ($n = 44$) for their counterparts in the control group.

CONCLUSIONS: Our study compared ASD group to controls in terms of birth order, demonstrating a significant difference for being the first-born child in the ASD group. Birth order can be considered to be one of the several environmental factors that will help in understanding ASD, in which environmental factors can be the cause of phenotypic complexity. For all that, in our study, it was observed that having a child with autism in the Turkish sample did not affect the decision for the next pregnancy.

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Autism; ASD; birth order; stoppage; environmental factors

Introduction

Autism spectrum disorder (ASD) is a developmental disorder characterized by impairment in social interactions and communication accompanied with restricted interest and repetitive behaviours [1]. The estimated prevalence of ASD varies between 0.9% and 2.7% [1] and has increased noticeably during the past 20 years [2]. Both clinical and epidemiological studies have shown that autism is four to five times more common in boys [3].

ASD is thought to have a genetic basis [4]; however, the exact mechanism and potential genes to be involved in the development of the disorder have not been identified, yet. Prenatal exposures to some environmental stimuli, too, have been suggested playing a role in the etiopathogenesis of ASD [5]. Among them, advanced maternal and paternal age, parity, birth order, and obstetric-related issues such as bleeding, preeclampsia, induced or prolonged labour, type of delivery, intrauterine meconium exposure, foetal distress, maternal drug use in pregnancy (i.e. psychotropic drugs), pre- and post-maturity, birth weight, low Apgar scores, and birth defects, have been the frequently studied parameters [5–9]. Although birth-order studies in psychiatric diseases maintain their popularity, there are no definite results identified, especially whether there is an association between autism and birth order [5,10,11]. Despite the presence of some studies claiming that ASD emerges in the first child, the results are considered as contradictory. There are some reports pointing out a negative correlation [11] or a positive correlation [12–14] between birth order and ASD, as well as others reporting that there was no relation between birth order and ASD [5].

Stoppage is defined as a phenomenon in which parents of a child with a severe disease tend to have fewer subsequent children or halt reproduction. Having an autistic child has been evaluated by many studies as a potential factor to affect subsequent pregnancy decisions of case families. In literature, there are studies reporting that the presence of an autistic child in a family affects the next pregnancy decision; however,

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some other studies present conflicting results. Hoffmann et al. [15] and Wood et al. [16] reported that having a child with ASD is associated with reproductive stoppage, whereas Grønborg et al. [17] reported contradictory results on the same issue.

In order to contribute to this area of research, we aimed to compare birth orders and the number of siblings of children with ASD to those of a control group. We investigated the risk factors, too, in the etiopathogenesis of ASD by assessing the potential roles of the age and educational level of the parents, delivery type, and assisted reproductive techniques in addition to the assessment of the number of siblings and birth order. Furthermore, we assessed whether having an autistic child affects the decision-making for subsequent pregnancies or leads to the reproductive stoppage.

Methods

In total, 196 patients, who were diagnosed at our clinic with ASD according to DSM-5 criteria [18] between January 2015 and January 2016, were included in the study. The diagnoses were made by two psychiatrists specialized in child and adolescent psychiatry upon psychiatric examination. Simplex families were included to this study. Families those had known or suspected genetic syndromes were excluded from the study. The patients with chronic diseases or malignancies were also excluded from the study. The control group consisted of 54 healthy children who presented to the paediatric outpatient clinic for vaccination if their ages and genders matched with the study group. A family history and information about children's symptoms were obtained from the primary caregiver using standardized clinical forms. Turkish version of Autism Behavior Checklist (ABC) [19] and Aberrant Behavior Checklist (AbBC) [20] were administered to the primary caregivers of children with ASD. Another scale, which is Childhood Autism Rating Scale scores (CARS) [21] was administered by an experienced child and adolescent psychiatrist.

Maternal and paternal age and their educational levels, patient age, number of siblings, birth order, type of delivery at birth, assisted reproductive techniques, and the impact of both being the first-born child and having ASD on reproductive behaviour of case families were the parameters to be examined. Statistical analysis was performed via IBM SPSS Statistics for Windows, version 17.0 (Chicago Inc., 2008). All continuous variables were defined as means and standard deviations (SD), whereas categorical ones were assessed by frequencies and percentages. Comparisons were performed by Student's *T*-test or Mann–Whitney *U*-test, and Pearson chi-square test as its non-parametric equivalents. A "p" value of ".05" was considered as statistically significant. To conduct the study, the effect size was calculated with 1% precision and 5% alpha error for 1% frequency of ASD resulting in 180 of children with ASD and 50 of healthy children. Approval of the local ethics committee for this study also was obtained. Informed consent was obtained from all individual participants and their legal representatives.

Results

Demographics

The mean age of the patients ($n = 196$) and the controls ($n = 54$) were 56.9 months (SD 27.1 months; median: 51) and 55.7 months (SD 13.8 months; median: 54), respectively. There was no significant difference

Table 1. Demographics of the ASD and the control group.

	ASD group ($n = 196$) Mean (SD) *M* (mn–mx)	Control group ($n = 54$) Mean (SD) *M* (mn–mx)	Total ($n = 250$) Mean (SD) *M* (mn–mx)	χ^2	*p*
Age					
Child's (month)	56.9 (27.1) 51 (16–152)	55.7 (13.8) 54 (36–84)	56.7 (24.8) 51 (16–152)	−0.834	.404
Mothers' (year)	35.3 (6.5) 35 (22–54)	33.5 (4.2) 33 (23–42)	34.9 (6.1) 34 (22–54)	−1.134	.257
Fathers' (year)	39.0 (6.7) 38 (21–59)	37.6 (4.8) 36 (30–51)	38.6 (6.4) 38 (21–59)	−1.491	.136
	n (%)	*n* (%)	*n* (%)		
Gender					
Male	163 (83.2)	47 (87.0)	210 (84.0)	0.473	.492
Female	33 (16.8)	7 (13.0)	40 (16.0)		
Delivery					
Normal	110 (56.1)	27 (50.0)	137 (54.8)	0.641	.423
S/C	86 (43.9)	27 (50.0)	113 (45.2)		
IVF					
None	186 (94.9)	49 (90.7)	235 (94.0)	0.175[a]	.327
Yes	10 (5.1)	5 (9.3)	15 (6.0)		
Difficult labour					
No	154 (78.6)	52 (96.3)	206 (82.4)	9.171	.002
Yes	42 (21.4)	2 (3.7)	44 (17.6)		

Note: SD: standard deviation; Mn–mx: minimum–maximum; IVF: *in vitro* fertilization.
[a]Fisher's exact test.

between the two groups in terms of age ($p > .05$). The maternal and paternal ages of patients with ASD was higher than those of controls, though there was no statistical significance ($p > .05$) (Table 1).

In the ASD group, 163 patients (83.2%) were males and 33 patients (16.8%) were females. In the healthy control group, 47 children (85.1%) were males and 7 children (14.9%) were females. There was no significant difference between the two groups in terms of gender ($p > .05$).

The rates of spontaneous vaginal delivery and Caesarean section (C-section) were similar between the patients and the controls ($p > .05$). The rates of assisted reproductive techniques (including *in vitro* fertilization) were similar between the groups ($p > .05$). Difficulties experienced during labour (prolonged labour, vacuum, or forceps-assisted vaginal delivery) were significantly higher in the ASD group than the controls (21.4% versus 3.7%, respectively; $p = .002$) (Table 1).

Birth order

As regards to birth order, 63.3% ($n = 124$) of the patients with autism were the first-born children, 26.0% ($n = 51$) were the second, 7.7% ($n = 15$) were the third, 2.6% ($n = 5$) were the fourth, and 0.5% ($n = 1$) were the fifth child in their families ($\chi^2 = 15.729$, $p = .003$). Because there were no children in the control group born as the fourth or the fifth child in their families, those children were excluded from the analysis. When data were re-analysed by excluding children born on the fourth and fifth birth-order ranks, the result was statistically significant for being the first-born child in ASD group compared to the control group ($\chi^2 = 13.792$, $p = .001$). Dual comparisons indicated that being a first-born child with ASD was a statistically significant parameter among other comparisons in respect to the control group ($\chi^2 = 12.028$, $p = .001$) (Table 2).

Birth order versus demographics

Regarding the association between gender and birth order, the rate of being a female in the first-born children in ASD group was found to be statistically higher than that of the control group (Fisher's exact test = 14.338, $p = .002$). Evaluating the type of delivery at birth and birth order revealed a significantly higher C-section rate in first-born children in the ASD group compared to that of the control group (Fisher's exact test = 8.035, $p = .032$).

The proportions of the first-born children delivered after a prolonged labour or by vacuum-forceps applications in ASD group were significantly higher compared to the control group (Fisher's exact test = 9.429, $p = .024$, Table 3).

Stoppage

The proportion of having a single child was 14.4% for all subjects (36/250). While 13.3% of the families (26/196) in ASD group had one child, 18.5% of families (10/54) in the control group had one child, revealing a statistically not significant result for stoppage ($\chi^2 = 0.948$, $p = .330$). It was found that 86.7% ($n = 170$) of the children in the ASD group had at least one sibling compared to the rate of 81.5% ($n = 44$) for their counterparts in the control group (Table 4).

Other analyses

Within the ASD group, there was no correlation between the number of siblings or the birth order and the ABC, AbBC or CARS scores ($p > .05$ for all variables).

Discussion

The birth order, which is defined as the order of arrival among the siblings of the individual, has been investigated in many disease aetiologies in recent years [22]. There are different results and interpretations in the literature with respect to the relation between birth order and ASD. Our study compared ASD group to controls in terms of birth order, demonstrating a significant difference for being the first-born child in the ASD group. Reviewing the research carried out in this area, a study in which pregnancy complications were not controlled, reported that there was no association between ASD and maternal age or birth order [11]. However, other studies demonstrated a higher risk for ASD in the first-born children compared to the

Table 2. Children's birth orders analyses between autism spectrum disorder and the control group.

	ASD ($n = 196$) *n* (%)	Control ($n = 54$) *n* (%)	Total ($n = 250$) *n* (%)	First analysis		Dual comparisons	
				χ^2	*p*	1st vs. 2nd	
First	124 (63.3)	22 (40.7)	146 (58.4)	15.729	.003	12.028	.001
Second	51 (26.0)	29 (53.7)	80 (32.0)			1st vs. 3rd	
Third	15 (7.7)	3 (5.6)	18 (7.2)	After correction for 4th and 5th		0.304	
Fourth	5 (2.6)	0	5 (2.0)	χ^2	*p*	2nd vs. 3rd	
Fifth	1 (0.5)	0	1 (0.4)	13.792	.001	6.853	.032[NS]

Note: NS: non-significant points as $p > .017$.
[a]Fisher's exact test.

Table 3. Birth order versus demographics between autism spectrum disorder and control groups ($n = 250$).

		Birth order						
	Group	First *n* (%)	Second *n* (%)	Third *n* (%)	Fourth *n* (%)	Fifth *n* (%)	χ^2	*p*
Gender								
Male	ASD	102 (62.6)	45 (27.6)	13 (8.0)	3 (1.8)	0		
	Control	22 (46.8)	23 (48.9)	2 (4.3)	0 (0.0)	0	7.161[a]	.055
	Total	124 (59.0)	68 (32.4)	15 (7.1)	3 (1.4)	0		
Female	ASD	22 (66.7)	6 (18.2)	2 (6.1)	0 (0.0)	1 (3.0)		
	Control	0 (0.0)	6 (85.7)	1 (14.3)	0 (0.0)	0	14.338[a]	.002
	Total	22 (55.0)	12 (30.0)	3 (7.5)	0 (0.0)	1 (2.5)		
Labour								
Normal	ASD	68 (61.8)	29 (26.4)	10 (9.1)	2 (1.8)	1 (0.9)		
	Control	10 (37.0)	14 (51.9)	3 (11.1)	0 (0.0)	0 (0.0)	7.437[a]	.085
	Total	78 (56.9)	43 (31.4)	13 (9.5)	2 (1.5)	1 (0.7)		
S/C	ASD	56 (65.1)	22 (25.6)	0 (0.0)	3 (3.5)	–		
	Control	12 (44.4)	15 (55.6)	5 (5.8)	0 (0.0)	–	8.035[a]	.032
	Total	68 (60.2)	37 (32.7)	5 (4.4)	3 (2.7)	–		
Forced								
Vacuum or prolonged	ASD	32 (76.2)	6 (14.3)	2 (4.8)	2 (4.8)	–		
	Control	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	–	9.429[a]	.024
	Total	32 (72.7)	8 (18.2)	2 (4.5)	2 (4.5)	–		

[a]Fisher's exact test.

control subjects [12–14]. Our results confirm the reports of the latter studies.

It has been reported that during the first labour, the child is exposed to the birth canal stress, congenital complications, and asphyxia at a greater extent and more frequently, and that each of these factors might lead to minimal brain damage [23,24]. In our study, the rate of difficulties during labour was determined to be higher in the ASD group than that of the control group. Evaluation of these findings, that is the higher rates of being the first-born children and the higher rates of difficult labours in the ASD group, suggests that the first-born children may be more exposed to perinatal stress, resulting in minimal brain damage, which may have a role in ASD etiopathogenesis.

There are contradictory results on the potential role of maternal or paternal age in ASD. A cohort of ASD cases reported that the probability of developing autism in their third children, whose mothers' ages were between 20 and 34, and fathers' ages were below 40, was three-times higher than that of the first-born children of older parents [10]. In another study, the order of birth and maternal age in 113 families having children with ASD were compared with the general population. No correlation was reported for birth order in the ASD group. Especially risky pregnancies (including first, fourth or later births) demonstrated more autistic children compared to the population sample [25,26].

Examining the designs of the studies, in general, reveals some limitations such as inadequate selection of the control group, insufficient diagnostic tools, and lack of identification of delivery types at birth. In our study, the maternal and paternal ages were higher in the ASD group; however, this difference was not statistically significant. This result supports the findings of other studies reporting that parental age is not among the primary risk factors for having autistic children.

In our study, it was found that there were no statistically significant differences between birth order and sibling numbers and CARS, ABC, AbBC scores in the autistic group. A study with a small sample size including 16 families, reported that non-verbal IQ scores decreased as the number of births increased [27]. A different study with 161 families showed a significant increase in speech difficulties and repetitive behaviours in the first and second children, diagnosed with ASD, in these case families [28]. In the same study, it was observed that there was a negative correlation between birth order and intelligence level in children affected by autism. Another similar study suggested that difficulties in verbal and non-verbal communication were more common in autistic children born as the first and second children, and that autism-related symptoms were more severe in those subjects [29]. These studies demonstrate similar patterns and limitations, such as the inadequacy of the control groups, and the selection of study patients among the patients, who present to the clinic. Although our results are not parallel to those reported in the literature, the differences are interpreted to be due to cultural variabilities.

It was also found that 86.7% ($n = 170$) of the children in the autism group and (81.5%) ($n = 44$) of children in the control group had at least one sibling. It was

Table 4. The proportion of children by their number of siblings between autism spectrum group and control subjects ($n = 250$).

	ASD ($n = 196$) *n* (%)	Control ($n = 54$) *n* (%)	Total ($n = 250$) *n* (%)	χ^2	*p*
Only one child	26 (13.3)	10 (18.5)	36 (14.4)	0.948	.330[a]
At least one sibling	170 (86.7)	44 (81.5)	214 (85.6)		
One sibling	132 (67.3)	39 (72.2)	171 (68.4)		
Two siblings	28 (14.3)	5 (9.3)	33 (13.2)		
Three siblings	9 (4.6)	0	9 (3.6)		
Four siblings	1 (0.5)	0	1 (0.4)		

[a]Fisher's exact test.

determined that 92 (46.9%) mothers having autistic children did not give birth to others. However, it was observed that 53.1% (104/196) of the mothers continued to give birth even though they had autistic children. There are conflicting results in the literature whether having autistic children affects the decision for the next pregnancy [15–17]. These studies, published by Hoffmann et al. [15] in the US and by Wood et al. [16] in England, demonstrated that mothers with autistic children did not give birth to other children. However, another study published by Gronborg et al. [17] reported that Danish mothers with autistic children continued to give birth. Psychosocial implications of having children with ASD may cause fewer children in families by influencing the decision for the next pregnancy. In our study, it was observed that having a child with autism in the Turkish sample did not affect the decision for the next pregnancy.

We also investigated the relationship between gender, type of delivery (C-section or vaginal), and assisted reproductive techniques used for conception in the study groups. No study results on the sex of the first-born child with autism exist in the literature. Regarding to the method of deliveries, contradictory findings have been reported. It was emphasized in some studies that Caesarean sections increased the risk of ASD; however, it was reported to be lower in some other studies [30–33]. In the retrospective cohort study, birth history records were analysed, concluding that there was no significant difference between the type of delivery and ASD [33]. In another study, assisted reproductive techniques were demonstrated to be one of the risk factors for developing autism, but another study reported no significant difference [34,35].

In our study, by the statistical analysis including single-child families as well, the first-born autistic children were demonstrated at significantly higher rates among girls, Caesarean section cases, and forced deliveries. Our research findings provide supportive evidence that these factors are not the indicated associated risk factors for ASD [6,36].

There are some limitations of our study that it is not a community-based study as the study sample consists of patients applying to the clinic. The other limitation is the smaller size of the control group compared to the patient group. However, the results of community-based studies may demonstrate variabilities. Because of our study consisted of only simplex families, our results could not be generalized for multiplex families. Since our study included a control group, despite the small sample size compared to the patient group, the comparative analysis of the parameters including the type of deliveries at birth and one-child families to the control group are our study's strong aspects.

Although there have been reported studies pointing out that there is a significant relationship between birth order and autism, this relationship is not consistent and often not linear. There is a fundamental difficulty in enlightening this relationship between the birth order and autism, since the mother with autistic children does not prefer to give birth to another child. Thus, evaluating birth order in autism is naturally handicapped with the mothers had twin children with both autism or all children had autism. Despite the studies conducted in this area shed light on the link between autism and the birth order, the small sample sizes and lack of systematic evaluations limit the generalization of the results. The order of birth can be considered as one of the many environmental factors, which will help in understanding ASD. However, as it is well known, ASD has a complex and multifactorial aetiology. Environmental interactions apart from the birth order and genetics can also be the cause of phenotypic complexity in the ASD.

Compliance with ethical standards

The local ethics committee approval was obtained for the study. Local Ethics Committee approval for this study is registered as 2017-120.

Informed consent was obtained from all individual participants and their legal representatives included in the study.

Research involving human participants and/or animals: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Local Ethics Committee approval for this study is registered as 2017-120.

Disclosure statement

No potential conflict of interest was reported by the authors.

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