ORIGINAL ARTICLE

Prenatal Risk Factors of Autism Spectrum Disorder Compared to Congenital Visual and Hearing Loss: A Case-Control Study

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ABSTRACT

Objectives: Relations exist between autism spectrum disorder (ASD) and visual and hearing loss (VL/HL). This study evaluated the prenatal risk factors specific to ASD compared to VL/HL.

Materials & Methods: This case-control study recruited individuals with ASD to compare with individuals with VL/HL as controls from special schools. Parents completed a questionnaire containing questions about demographic characteristics, socioeconomic status, family history of neurological or psychological disorders, and problems during the pregnancy.

Results: Five hundred thirty-six participants were enrolled in the study, of which 238 (44.4%) had ASD, 198 individuals had HL (36.9%), and 100 had VL (18.7%). Seven (2.9%) participants in the ASD group were male, significantly ($p<0.001$) lower than the proportion of males in the HL/VL group (99, 33.2%). In the final regression model, higher educational levels of parents and gestational hypertension were associated with a higher risk of ASD ($p<0.05$). However, female gender, parents not living together, and cousin marriage were associated with a higher risk of HL/VL ($p<0.05$).

Conclusion: This preliminary study determined the factors more associated with ASD than HL/VL. Believably, the study's results could shed more light on the exclusive risk factors of ASD.

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Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by impaired social communication and restricted, repetitive patterns of behaviors, activities, and interests (1). Other typical signs of individuals with ASD include speech and language delay, regressions in developmental milestones at 18-24 months, tactile sensitivities, and disruptive, self-stimulating behaviors (2).

Pieces of evidence exist showing the co-occurrence of ASD with other neurodevelopmental disorders such as cerebral palsy (CP), intellectual disability (ID), and sensorineural impairments, including visual and hearing impairments (3-5). Available evidence shows the prevalence of ASD is higher among people with sensorineural impairments such as developmental hearing loss (HL) or visual loss (VL) than in the general population (6-9). Children affected primarily by ASD can experience a range of visual/hearing processing and perceptual deficits (8, 10). Similarly, children with HL or VL may experience cognitive impairments that mainly co-occur with ASD symptoms, such as socio-cognitive deficits, social isolation, and language deficits (9, 11-13). For instance, Chilosi et al., in a clinical study, investigated the comorbidity of neurodevelopmental disorders in children with severe to profound hearing loss (14). They reported that cognitive, behavioral–emotional,

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and motor disorders were the most frequent impairments in children with hearing loss.

Evidence represents potentially shared etiologies and risk factors that might infer co-occurrence between ASD and VL/HL. Retrolental fibroplasia, Leber's congenital amaurosis, and rubella have been identified as potential common risk factors for ASD and VL. Additionally, cytomegalovirus, toxoplasmosis, bacterial meningitis, rubella, and measles have been cited as potential shared etiologies for ASD and developmental HL (9, 15). Given all together, seemingly, at least in part, there have been associations between ASD and sensorineural processing deficits such as VL or HL, on the contrary.

Regarding the etiology of ASD, a complex set of genetic and environmental factors has been introduced in the literature(16). Twin and family research showed that genetic factors play a significant role in the etiology of ASD (17, 18). Besides, environmental factors, including prenatal risk factors such as advanced parental age and pregnancy-related factors (e.g., maternal obesity, diabetes, cesarean section, and the like), are likely involved in the pathogenesis of ASD(19, 20). For example, a recent study has identified advanced maternal age, prenatal bleeding, pre-eclampsia, prenatal pethidine usage, and fetal distress before birth as associated with increased risk of ASD in a sample of 4306 children (21). In another study, a recent systematic review reported that excessive maternal gestational weight gain might be associated with an increased risk of ASD in the offspring (22).

In sum, various ASD environmental risk factors have been evaluated in different investigations (23-25). Therefore, a need exists to narrow or specify the environmental risk factors by administering different control groups. In most studies, individuals with ASD have been compared with children with typically developed (TD) to determine the potential risk factors. As described earlier, since VL/HL may be associated with some aspects of ASD characteristics, and developmental deficits are present in both ASD and visual/hearing impairments, this study aims to verify findings in the previous risk factor studies by using new control groups. Thus, the current study evaluated prenatal risk factors in ASD compared to children with other developmental disorders such as VL and HL. The present study selected several perinatal factors that have been shown to play a role in the etiology of ASD in previous studies. These factors included the child and parents' sociodemographic information, psychological/ neurological history of first-degree relatives, and pregnancy-related factors. Supposedly, the current study's results shed more light on the exclusive risk factors of ASD compared to HL/VL.

Materials & Methods

This study conducted a case-control study on people with a confirmed diagnosis of ASD, VL, and HL in special schools in Tehran, Iran. The Research Ethics Committee of the university approved the study protocol (ethic code: IR.TUMS.NI.REC.1399.053). Written informed consent was obtained from the parents after the research goals and procedures were explained to them.

Participants

The participants were recruited based on the convenience sample of students in special schools (i.e., schools of children with special needs) in Tehran, Iran. These special schools have students of both genders with an age range of five years and older. The participants were invited to the study through advertisements in the special education system and by attending briefing sessions for families, caregivers, and teachers held at the school. In-person and private briefing sessions were also held in case some families needed further explanations. A pediatric physician confirmed the diagnosis of ASD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (DSM-5) criteria (26). Congenital VL was defined as having a visual acuity of less than 0.05 or a visual field of ten degrees or less by a licensed optometrist. In addition, congenital HL was characterized by bilateral HL greater than 20 dB HL. A licensed audiometrist confirmed congenital HL. Individuals with a concurrent diagnosis of ASD and either HL or VL were excluded from the study. Two hundred thirty-eight individuals diagnosed with ASD were successfully enrolled, with an average age of 11.4 years, serving as the case group, while 298 individuals, representing 55.6%, with either VL or HL, had a mean age of 13.7 years and constituted the control group.

Variables

The study questionnaire included questions on participants' demographic and socioeconomic characteristics, problems during pregnancy, and history of neurological or psychological disorders in first-degree relatives. Two experts provided additional explanations or clarification to comprehend the questions if necessary.

Basic demographic variables encompassed gender, age at the time of the study, age at the time of diagnosis, whether the individual resulted from an unwanted pregnancy, and whether the parents were cousins. Socioeconomic status and familial questions encompassed items about parents' age, marital status (living together or other statuses), family home ownership (owner-renting or other), parents' current occupations, and parents' educational levels. Educational level was classified into three groups: Lower than a high school diploma, a high school diploma (equal to 11 years of education), and higher than a high school diploma.

Questions on pregnancy-related problems included items on excessive weight gain, weight loss, nausea or vomiting for more than three months, spotting or mild vaginal bleeding, excessive bleeding requiring medical attention, infection requiring medical attention, hypertension, using medications, and family problems during pregnancy. Furthermore, questions were asked regarding the type of delivery—either vaginal or cesarean—and whether the delivery was early or delayed. This study evaluated the history of neurological or psychological problems in first-degree relatives, including parents and siblings. These disorders included a history of attention-deficit/hyperactivity disorder, other psychological disorders, learning difficulties, speech disorder, and other disorders.

Statistical analysis

The mean and standard deviation (SD) were calculated for quantitative variables. We used the Kolmogorov-Smirnov test to evaluate whether each variable's values are distributed normally or not. As all quantitative variables were not distributed normally (P<0.05), this study used non-parametric tests such as Mann-Whitney and Kruskal-Wallis tests to evaluate the differences between cases and controls in terms of quantitative variables. The present study calculated the number and percentage in each group for categorical variables. This research used the Chi-square test to evaluate the differences in the distribution of categorical variables in cases and controls. Multiple backward stepwise binary logistic regression analyses were used to identify factors independently associated with ASD development, enabling the prediction of ASD incidence. All variables, except age at the time of diagnosis and age at the time of study, were included in the initial model. A p-value of less than 0.05 is considered statistically significant. All analyses were performed using SPSS version 26.

Table 1. Demographic characteristics and socioeconomic characteristics of participants

Variables		Autism spectrum disorders (n=238)	Hearing loss/visual loss (n=298)	P-value
Gender	Male	231 (97.1%)	199 (66.8%)	<0.001
	Female	7 (2.9%)	99 (33.2%)	
Age (years)		11.4 (2.8)	13.7 (4.6)	<0.001
Age at the time of the diagnosis (months) (n=473)		34.8 (18.8)	14.3 (19.7)	<0.001
Parents marital status	Together	219 (93.2%)	239 (90.2%)	0.227
	Other	16 (6.8%)	26 (9.8%)	
Father's age (year) (n=433)		44 (6.7)	43.2 (6.8)	0.122
Mother's age (year) (n=448)		38.4 (6.5)	38.2 (7)	0.647
Father's educational level	Less than a high school diploma	38 (16%)	134 (45%)	<0.001
	High school diploma	69 (29%)	62 (20.8%)	
	More than a high school diploma	131 (55%)	102 (34.2%)	
Mother's educational level	Less than a high school diploma	37 (15.5%)	131 (44%)	<0.001
	High school diploma	80 (33.6%)	94 (31.5%)	
	More than a high school diploma	121 (50.8%)	73 (24.5%)	
Father's job	Employed	210 (92.5%)	228 (91.2%)	0.602
	Other (student, unemployed, retired)	17 (7.5%)	22 (8.8%)	
Mother's job	Employed	50 (21.9%)	35 (13.5%)	0.014
	Other (student, unemployed, housewife)	178 (78.1%)	225 (86.5%)	
Family home ownership	Owner	123 (54.4%)	104 (41.4%)	0.005
	Renting or other	103 (45.6%)	147 (58.6%)	
Cousine marriage	No	168 (73.4%)	132 (50%)	<0.001
	Yes	61 (26.6%)	132 (50%)	
Unwanted pregnancy	No	146 (62.9%)	148 (56.3%)	0.132
	Yes	86 (37.1%)	115 (43.7%)	

Values are reported as number (percentage), except for age, father's age, and mother's age, which are reported as mean (SD).

Results

Five hundred thirty-six participants were enrolled in the study, of which 238 (44.4%) had ASD, 198 individuals had HL (36.9%), and 100 had VL (18.7%). Seven (2.9%) participants in the ASD group were male, significantly (p<0.001) lower than the proportion of males in the HL/VL group (99, 33.2%). Similarly, participants in the ASD group were diagnosed at older ages (34.8 vs. 14.3 months, p<0.001), their parents had higher educational levels (p<0.001), a higher proportion of their mothers were employed (21.9% vs. 13.5%, p=0.014), a higher proportion of their families owned a home (55.4% vs. 41.4%, p=0.005), and a lower proportion of their parents were cousins (26.6% vs. 50%, p<0.001) compared to children in the HL/VL group (Table 1)

Problems during the pregnancy are compared between groups in Table 2. Excessive weight gain (13% vs. 6.4%, p=0.009), spotting or mild vaginal bleeding (19.3% vs. 8.4%, p<0.001), infection (6.3% vs. 2.3%, p=0.022), hypertension (9.7% vs. 3.4%, p=0.003), use of medication by mother (17% vs. 10.7%, p=0.041), and cesarean delivery type (72.5% vs. 49.2%, p<0.001) were more common in the ASD group compared to the HL/VL group.

Table 2. Comparison of health issues during pregnancy between the groups

Variables		Autism spectrum disorders (n=238)	Hearing loss/visual loss (n=298)	P-value
Excessive weight gain		31 (13%)	19 (6.4%)	0.009
Weight loss		12 (5%)	19 (6.4%)	0.511
Nausea or vomiting for more than three months		60 (25.2%)	65 (21.8%)	0.355
Spotting or mild vaginal bleeding		46 (19.3%)	25 (8.4%)	<0.001
Excessive bleeding requiring medical attention		19 (8%)	13 (4.4%)	0.079
Infection requiring medical attention		15 (6.3%)	7 (2.3%)	0.022
Hypertension		23 (9.7%)	10 (3.4%)	0.003
Other problems		40 (16.8%)	34 (11.4%)	0.072
Mother using medications		39 (17%)	28 (10.7%)	0.041
Family problems		55 (24.9%)	49 (19.7%)	0.175
Early or delayed delivery		90 (39.1%)	99 (37.4%)	0.686
Delivery type	NVD	64 (27.5%)	130 (50.8%)	<0.001
	Cesarean	169 (72.5%)	126 (49.2%)	

Values are reported as number (percentage).

Table 3. Comparing the family history of neurological, psychological, and learning problems between groups

Variables	Autism spectrum disorders (n=238)	Hearing loss/visual loss (n=298)	P-value
Speech disorder	13 (5.5%)	23 (7.7%)	0.3
ADHD	26 (10.9%)	18 (6%)	0.041
Other psychological disorders	36 (15.1%)	24 (8.1%)	0.01
Learning difficulties	58 (24.4%)	72 (24.2%)	0.955
Other disorders	16 (6.7%)	9 (3%)	0.043

Values are reported as number (percentage)

Table 4. Results of multiple stepwise backward binary logistic regression tests to determine the factors associated with a higher risk of ASD (visual/hearing loss group was the reference)

Variables		Odds Ratio	95% Confidence	P-value
Female gender		0.08	0.034-0.189	<0.001
Parents not living together		0.318	0.143-0.709	0.005
Father's educational level	Less than a high school diploma (reference)	*	*	*
	High school diploma	2.62	1.448-4.74	0.001
	More than a high school diploma	2.939	1.598-5.404	0.001
Mother's educational level	Less than a high school diploma	*	*	*
	High school diploma	1.676	0.951-2.953	0.074
	More than a high school diploma	4.353	2.228-8.504	<0.001
Cousine marriage		0.505	0.321-0.794	0.003
Gestational hypertension		2.99	1.075- 8.313	0.036

Table 3 compares the family history of neurological, psychological, and learning problems between groups. Family history of ADHD (10.9% vs. 6%, p=0.041) and other psychological issues (15.1% vs. 8.1%, p=0.01) were more common in the ASD group compared to the HL/VL group. However, no differences were found between groups regarding the family history of speech disorders and learning difficulties (p>0.05).

Results of multiple stepwise backward binary logistic regression tests to determine the factors associated with a higher risk of ASD are shown in Table 4. In the final model, higher educational levels of parents and gestational hypertension were associated with a higher risk of ASD (p<0.05). However, the female gender, parents not living together, and cousin marriage were associated with a higher risk of HL/VL (p<0.05).

Discussion

A substantial amount of evidence has investigated the possible risk factors associated with ASD(20). b However, to our knowledge, this study is unique in its assessment of these potential risk factors for individuals with ASD in comparison to other developmental disabilities, such as VL or HL. In line with previous evidence, we found a few specific risk factors of ASD compared to the control group. The obtained findings showed that gestational hypertension was independently related to the ASD diagnosis compared to HL/VL. In addition, parents' educational level was also found to be an independent risk factor for ASD.

Regarding demographic assessment, the present results suggested that parents' higher educational level is associated with a higher risk of ASD compared to HL/VL. In agreement, a classic epidemiologic survey in the United States found that most parents of individuals with ASD had a diploma or higher educational degree (27). Moreover, Baron Cohen et al. reported that there may be a possible link between genes contributing to autism and genes supporting technical aptitude (28). Cohen stated that the offspring of scientists and systemizers might inherit genes that not only transfer intellectual abilities but also expose them to ASD (28). However, we should be cautious in such an interpretation. Future studies are required to clarify the association between parental intelligence or education and the potential risk of ASD in the offspring. Another possible explanation could be that people have a stigma toward individuals with ASD. Parents with lower socioeconomic status perceived higher levels of stigma (29) and may have less intention to seek medical care. They may attempt to isolate their children with ASD. Thus, parents' higher awareness of ASD plays a key role in diagnosing ASD(30, 31), which may be why they seek medical care sooner and have a higher rate of ASD diagnosis in their children. In Iran, a mandatory free screening program exists for all children, regardless of socioeconomic status, to detect auditory and visual impairment in early childhood. It may lead to higher detection of children with VL or HL than ASD among people with low socioeconomic status. Although some controversial data from Sweden and Denmark show that parents' lower educational level was associated with ASD in offspring (32, 33), we could replicate the findings of the American population in a developing country and a new sample with ASD.

Gestational hypertension is another factor that this study found to have associations with ASD compared to visual and hearing impairments. Interestingly, two recent studies showed that pregnancy-induced hypertension may not be considered a risk factor for VL or HL (34, 35). However, earlier findings had suggested that gestational hypertension could be associated with hearing impairment (36) or retinopathy of prematurity, one of the leading causes of childhood blindness (37). Moreover, a large body of evidence is available representing the increased risk of some specific neuropsychiatric disorders, such as cognitive impairment, schizophrenia, and ASD, with hypertensive disorders of pregnancy (38-40). One of the possible explanations could be that pregnancy-related hypertensive disorders may alter brain structural and vascular anatomy in a way that influences the pathways of neural and cognitive development, as Ratsep et al. suggested in their study (41). In a recent systematic review and meta-analysis, Xu et al. have represented a possible link between gestational hypertension and changes in brain structure (40) related to an increased risk of ASD in offspring (41). Changes in the growth of the neonate's brainstem and cerebellum due to gestational hypertension, associated with ASD, may be another explanation for the development of ASD (41, 42). Interestingly, to extend previous findings, this study highlighted that gestational hypertension has a stronger association with ASD than HL or VL. However, further studies are required to clarify the association between pregnancy hypertension and brain network alterations in the offspring.

Limitations and future research

Although this study highlighted the risk factors of ASD in a novel comparison to sensory and developmental disorders, there are a few limitations. A significant limitation of the present findings is the study's retrospective nature, which can raise a critique about the possible ambiguity between risk factors and differentiating or association factors of ASD. Thus, we recommend prospective studies to re-evaluate these factors for ASD compared to other neurodevelopmental disorders. In that vein, registries may help to conduct future large-scale studies to determine the potential specific risk factors of ASD. Further investigation is also appreciated to find how an array of such risk factors can be utilized to differentiate ASD from other neurodevelopmental disorders at the early stages of development.

In Conclusion

This preliminary study found that gestational hypertension and higher educational levels of parents are associated with a higher risk of ASD compared to HL/VL in a sample of Iranian students with ASD, VL, and HL. Believably, the present findings may be imperative for two specific reasons. First, as developing global knowledge from the diverse population is essential, this study has examined individuals with ASD from a developing country in the Middle East, a part of the world in which ASD is not comprehensively studied. Second, it potentially expands our understanding of the factors exclusively associated with ASD compared to other neurodevelopmental disorders such as HL and VL.

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Authors' Contributions

Mohammad Ali Mansournia: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Editing

Amin Nakhostin-Ansari: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Editing

Monir Shayestehfar: Data curation, Investigation, Project administration, Writing – original draft

Amir Hossein Memari: Formal Analysis, Investigation, Writing – original draft, Editing

Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

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