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Original article

Prenatal, Natal, and Neonatal Risk Factors Associated with Autism

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The complex neurodevelopmental illness known as autism spectrum disorder (ASD) first manifests in infancy or early childhood. ASD is influenced by both hereditary and non-genetic factors, which can work alone or in combination, leading to the disorder. The study aims to investigate the potential associations of several maternal, prenatal, and neonatal risk factors among autism children attending the National Center for autism diagnosis and Treatment in Tripoli, Libya, from August 2023 to January 2024. A cross-sectional study included 53 mothers of children diagnosed with autism attending the National Center for autism diagnosis and Treatment. The data were obtained using an interview-based questionnaire, which included data related to maternal, prenatal, and neonatal risk factors. Of the 53 autistic children (73.6%) who were male and 26.4% who were female. Maternal age above 20 at delivery was noted in 96.2% of the cases. Fetal distress, fever, and gestational diabetes were the most frequent prenatal risk factors (13.2%, 11.3%, and 9.4%, respectively); multiple deliveries, reported in three women, were the most common natal risk factor; and 32.1% of children had jaundice as a postnatal risk factor. Vitamin D deficiency (22.6%) and a history of obesity (13.2%) were the most frequent maternal comorbidities. In children with autism, there is an increased prevalence of obstetric and postnatal risk factors.

Introduction

The complex neurodevelopmental illness known as autism spectrum disorder (ASD) first manifests in infancy or early childhood. ASD is influenced by both hereditary and non-genetic factors, which can work alone or in combination, leading to the disorder. The World Health Organization lists abnormal interests, rigid or repetitive activities, impaired social and communication skills, and variations in sensory stimuli perception as characteristics of autism spectrum disorder (ASD) [1]. In individuals who suffer from ASD, behavioral and mental health issues are common and have significant consequences. A growing variety of research shows that ASD is frequently linked to mood disorders, suicidality, catatonia, psychosis, obsessive-compulsive disorder, self-harming behaviors, aggression, ADHD, anxiety, gender dysphoria, and schizophrenia spectrum disorders. There can be overlap between the fundamental characteristics of ASD and the symptoms of other behavioral and mental disorders that frequently affect individuals who have ASD, which makes diagnosis challenging [2].

With a 4:1 male-to-female ratio, over 800 genes linked to the condition, hundreds of chromosome abnormalities, hundreds of recognized syndromes, and a complicated interaction between inheritance and environmental factors impacted by epigenetics, ASD is a heterogeneous genetic disorder [3]. Individual characteristics, such as age, sex, intellectual ability, and genetic variables, increase the risk for co-occurring behavioral and psychiatric problems [4], with the bulk of studies currently focusing on children and adolescents with ASD [5]. Perinatal and prenatal elements few important risk factors were identified in a recent meta-analysis of prenatal factors that was restricted to pregnancy-related factors [6]. Maternal medicine, maternal hemorrhage during pregnancy, and gestational diabetes are the main contributing factors. We'll talk more about the latter topic later. Furthermore, compared to children born third or later, first-born children and children of foreign-born mothers in Nordic nations were found to be at higher risk in this meta-analysis. Based only on the four studies that employed sibling controls or adjusted for various factors, the analysis revealed a substantial increase in risk for autism related to exposure to intrauterine infections. The results using rat models of the maternal infection provide more evidence for the strong correlation between autism risk and maternal infection. These animal models simulate gestational viral infection by administering a synthetic double-stranded RNA called Poly I:C systemically, which triggers an innate immune response. It appears that viral infections during pregnancy trigger off a mother's immune system, which can interfere with the development of the fetus's brain, at least partially, by producing interleukin-6 [7].

The same authors identified a number of potential risk factors in a second meta-analysis that concentrated on the perinatal and neonatal period [8]. These factors included meconium aspiration, low birth weight,

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small for gestational age, low 5-minute Apgar score, neonatal anemia, ABO or Rh incompatibility, fetal distress, multiple births, birth injury or trauma, and summer birth. It would be more appropriate to see the previously described congenital malformations and feeding issues as signs of an underlying etiology of autism. The findings of a new study demonstrating that maternal illness in the first trimester increases autism risk are consistent with the identification of summer birth as a risk factor [9]. Status socioeconomic. While a study conducted in 1987 found no correlation between the risk of autism and socioeconomic position, including the education level of mothers, the latter may have a major impact on the age at which a child learns to speak on their own [10]. Furthermore, as was previously indicated, a meta-analysis revealed a considerably higher risk of autism in children whose moms were born outside of the country [6]. This risk was further outlined in a very recent study [11], which found that children of immigrants have a lower risk of high-functioning autism and a higher risk of autism with intellectual disability, particularly when parents immigrated to Sweden from areas with a low human development index.

The peak risk period for low-functioning autism was during pregnancy and the period of migration. These findings can be explained by a variety of reasons, including inadequate immunity to common illnesses or high levels of maternal stress.

Drug use and exposure to toxins, as previously mentioned, the most recent meta-analyses revealed that taking medication while pregnant increased the chance of autism [6]. One known risk factor for ASD is prenatal valproate exposure, particularly during the first trimester of pregnancy. Infants who are exposed to valproate during pregnancy are eight times more likely to have ASD [12]. Antidepressant use is one of the main worries about pharmaceutical exposure during pregnancy, as the percentage of pregnant women taking selective serotonin reuptake inhibitors climbed from 1.5% in 1996 to 6.4% in 2004 and 6.2% in 2005 [13]. Pregnancy-related exposure to antidepressants has been found to slightly raise the risk of ASD, particularly during the first trimester [14]. Last but not least, it was shown that prenatal exposure to the organophosphate pesticide chlorpyrifos increased the chance of ASD and that further research should be done on synthetic chemicals [15]. The study aims to investigate the potential associations of several maternal, prenatal, and neonatal risk factors among autism children attending the National Center for autism diagnosis and treatment in Tripoli, Libya, from August 2023 to January 2024.

Methods

Study design and period

The study was designed as a cross-sectional study and was conducted at the National Center for autism diagnosis and Treatment in Tripoli, Libya, from August 2023 to January 2024.

Study population and sampling

Convenient sampling of all mothers with children attending the National Center for autism diagnosis and treatment during the study period.

Inclusion and exclusion criteria

All participants who were diagnosed with ASD and had been confirmed by either a child psychiatrist or pediatrician were included. Furthermore, we only included participants who gave their consent to participate in the study. However, we had excluded patients who refused to participate in the study.

Study tool

The data were obtained using an interview-based questionnaire, which included the following sections**:** maternal factors, including the mother's age and blood group; prenatal factor: maternal mental illness, epilepsy\epilepsy medication, obesity, hypertension, DM, PCO, asthma, infection, vitamin D deficiency, assistant fertility, twins' pregnancy; perinatal factors: - abnormal presentation, fetal distress, umbilical cord complication, birth injury\trauma, low birth wight, congenital malformation, low 5 min Apgar score, meconium aspiration, neonatal anemia, neonatal convulsion.

Data management and analysis

The collected data were sorted, coded then entered and analyzed using the SPSS, version 25.0 statistical software. Descriptive statistics were used to summarize the outcome variables.

Ethical considerations

Permission was obtained from the health authority. The objectives of the study, expected benefits, and types of information to be collected were explained to all participants, and informed consent was obtained from each participant. The data collection tools used were anonymous, and data confidentiality was maintained.

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Results

Demographic Characteristics of Study Participants

This study included mothers of 53 children with autism (39 (73.6%) males and 14 (26.4%) females. Regarding the age of mothers, the majority (96.2%) were older than 20 years old, and only two (3.8%) were younger than 20 years old, as shown in Table 1. Twenty-six (49.1%) of mothers were blood group B+, twenty-four (45.3%) were blood group O+, and only three mothers (5.6%) were blood group B+.

Table 1. Characteristics of mothers of children with autism

Item		Frequency	Percentage
Maternal age			
	Younger than 20 years	2	3.8%
	Older than 20 years	51	96.2%
Mother blood group			
	Blood group O^+	24	45.3%
	Blood group A^+	26	49.1%
	Blood group B^+	3	5.6%

Antenatal risk factors

Table 2 shows the distribution of prenatal risk factors in children with autism diagnoses. Three mothers (5.7%) reported having pregnancy-induced hypertension, five (9.4%) reported having gestational diabetes, six (11.3%) reported having a fever, and seven (13.2%) reported experiencing fetal distress.

Table 2: Distribution of antenatal risk factors in children with Autism.

Item	Yes		No	
	F	%	F	%
Pregnancy-induced hypertension	3	5.7%	50	94.3%
Fetal distress	7	13.2%	46	86.8%
Gestational diabetes	5	9.4%	48	90.6%
Fever	6	11.3%	47	88.7%

Natal risk factors

Table 3 revealed that the most prevalent natal risk factors for autism among the mothers of the patients under study were multiple deliveries reported in three women (5.7%), followed by umbilical cord problems reported in one mother (1.9%). No mother had an atypical presentation, a birth injury, or birth asphyxia.

Table 3: Distribution of natal risk factors in children with Autism

Item	Yes		No	
	F	%	F	%
Birth asphyxia	0	0.0%	53	100.0%
Normal presentation	53	100.0%	0	0.0%
Umbilical cord complications	1	1.9%	52	98.1%
Multiple births	3	5.7%	50	94.3%
Birth injury	0	0.0%	53	100.0%

Postnatal factors

Table 4 showed that just 5 of the children had low birth weights and that the most common postnatal cause in 17 (32.1%) of their children was jaundice. Mothers' aspirations for meconium and neonatal convulsions have not been documented.

Table 4: Distribution of post-natal risk factors in children with Autism

Item	Yes		No	
	F	%	F	%
Birth weight	5	9.4%	48	90.6%
Jaundice	17	32.1%	36	67.9%
Neonatal seizures	0	0.0%	53	100.0%
Meconium aspiration	0	0.0%	53	100.0%

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Maternal comorbidities

It was observed that one mother (1.9%) reported having epilepsy, two mothers (3.8%) reported having bronchial asthma, and seven (13.2%) had a history of obesity. Additionally, seven (13.2%) had a PCO, and twelve (22.6%) had a vitamin D deficiency.

Table 5: Maternal comorbidities among the studied group.

Item	Yes		No	
	F	%	F	%
Vit D deficiency	12	22.6%	41	77.4%
Obesity	7	13.2%	46	86.8%
PCO	7	13.2%	46	86.8%
Bronchial asthma	2	3.8%	51	96.2%
Epilepsy	1	1.9%	52	98.1%

Discussion

The findings of this study evaluate the relationship between the mothers' age and blood group, among other demographic traits, and their diagnosis of autism spectrum condition. Fetal distress, gestational diabetes, fever, and pregnancy-induced hypertension are some of the antenatal risk factors and their correlations that have been identified. The natal risk factors that are included in our study are birth injury, multiple births, birth asphyxia, and umbilical cord complications. In addition, we evaluated meconium aspiration, low birth weight, jaundice, and newborn seizures as postnatal risk factors. Lastly, we looked for any correlations between autism and maternal comorbidities like as vitamin D deficiency, obesity, polycystic ovarian syndrome, bronchial asthma, and epilepsy.

The role of advancing maternal age in the etiology of autism has been debated [16,18]. This metanalysis support the assertion that advancing maternal age at the time of birth is associated with an increasing risk of autism in the offspring was robust to adjustment for confounding including paternal age, obstetric complication, birth year, birth order, and markers for socio-economic status, with offspring mother older than 35 years having 30% increased risk for the developing autism [11]. Our study supports these results by the frequency of mothers with an age above 20 years, about 51 (96.2%) of the study's sample.

The intricate pathophysiology of ASDs has been the subject of numerous investigations [19]. In this work, we hypothesized that a certain blood type of parents may influence a child's likelihood of developing autism through an unidentified genetic mechanism that then impairs fetal neurodevelopment. The distribution of ABO blood types among parents of children with ASD and the control population, however, did not differ significantly. This result has significant implications for other hematological and genetic research and strengthens the body of evidence showing there is no causal relationship between blood type and childhood ASDs [20]. Although our study shows that about 26(49%) of mothers are blood group A+, which reflects a good sample size of our research but the previous study shows the opposite result, which necessitates further investigation.

Consistent with earlier research, this cross-sectional study classified gestational diabetes as a risk factor with a frequency of 5 (9.4%) [21-23]. Gestational diabetes has been linked to increased incidence of pregnancy problems and unfavorable effects on fetal growth, according to a prospective study.[24] Additionally, it affected the development of fine and gross motor skills, which in turn resulted in learning disabilities and attention deficit hyperactivity disorder [24]. The increased oxidative stress experienced by the fetus during pregnancy and the epigenetic modifications in the expression of several genes may be the cause of these detrimental effects of maternal diabetes on the brain [25]. Furthermore, rather than the difficulties associated with hyperglycemia, the reported risk in maternal diabetes may be attributable to pregnancy complications. It is yet unclear if managing diabetes might lessen this correlation [24].

According to a study, increased levels of TNFα in the mother's bloodstream activate NFκB signaling, which in turn causes ASD-like phenotypes in children exposed to PE moms. TNFα neutralization improves neurodevelopmental outcomes, lessens ASD-like symptoms in offspring of PE moms, and restores NFκB signaling activation. This study further emphasizes how maternal inflammation contributes to negative neurodevelopmental outcomes in a PE model [26]. Furthermore, our transcriptome study of the adult male mice's hippocampi showed that PE had long-term negative impacts on progeny, most likely through modifications to the RA signaling and/or axonal guidance pathway. Simultaneously, these findings presented several new possible targets to address ASD-like symptoms in the progeny of PE model mice. According to Hu Ronggui and colleagues, Ube3a hyperactivity degrades Aldh1a2, an enzyme that limits the rate at which RA is synthesised, and is responsible for 1-3 percent of ASD cases globally. In mice with overexpression of Ube3a, RA supplementation dramatically reduces ASD-like behaviors [27]. Although our study's results support earlier findings, 5.7% [3], the sample size was a limitation.

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We investigated the potential link between autism spectrum disorder (ASD) and prenatal maternal immune activation. Our findings corroborate earlier claims that fever and maternal immunological activation are risk factors for ASD, 11.3% [6]. Our research, which links fever to an increased risk of ASD, is in line with the findings of Zerbo et al. [28], using antipyretics such as acetaminophen reduces the fever-ASD relationship, lending credence to this. Fever may, however, be a symptom of a particular infection that is linked to an increased risk of ASD but is not included in our questionnaire data, rather than fever itself being a part of the causal ASD pathway.

Whitehouse et al. (2013) looked at the connection between the autistic phenotype in the kids at ages 5-, 8-, 10-, and 14-year follow-up and the mother's 25(OH)D concentrations at 18 weeks of pregnancy [29]. After adjusting for several factors, including maternal education, socioeconomic status, race, age at conception, smoking during pregnancy, alcohol consumption during pregnancy, parity, infant health, and sex, the authors did not find any difference in 25(OH)D concentrations between mothers of children with and without clinical ASD (n = 929). The fact that just three boys received a clinical diagnosis of ASD at follow-up should be emphasized, and it is important to use caution when extending these findings to the larger ASD population. The total score and four of the five subscales of the Autism Like Quotient (autistic-like features) among 406 kids did not correlate with the maternal 25(OH)D concentrations. Even after adjusting for a number of possible confounders, such as the season of blood collection, children of mothers in the lower tertile (25(OH)D <45 nmol/L) had higher scores on the attention switching subscale (OR 5.46, 95% CI, 1.29–23.05, $p < 0.05$) than children of mothers in the higher tertiles [30,31]. In contrast to our study, which shows an increased likelihood of autism among individuals born to mothers who had vitamin D deficiency. 22.6% (12).

The majority of studies that have examined a link between high maternal BMI and childhood diagnosis of ASD have found a significant positive association [adjusted odds ratios (ORs) range from 1.5 to 1.7]. [32–33] This risk may be further augmented by intrauterine growth restriction,[34] preterm birth, high GWG, gestational or pre-gestational diabetes, and preeclampsia. A recent large retrospective case–control study reported a J-shaped association between maternal BMI and ASD, with both maternal underweight {AOR 1.43 [95% confidence interval (CI) 1.01, 2.04]} and maternal obesity [AOR 1.54 (95% CI 1.26–1.89)] significantly associated with ASD in offspring [35]. Interestingly, the possibility of comorbidity between PCOS and autism has been investigated in two earlier investigations. PCOS was more frequently reported by women with ASD than by mothers of children with ASD, according to Ingudomnukul et al. [36]. However, this finding is ambiguous and may be explained by a lack of statistical power. Our study, however, showed no significant association, and this needs more investigation.

Even though preterm delivery and LBW have been repeatedly identified as risk factors for neurodevelopmental impairment [37]. This was not supported by our findings. Research looking into the relationships between ASD and birth weight has shown generally similar findings, suggesting that LBW carries a higher risk [34]. Additionally, Schendel and Bhasin discovered that LBW girls exhibited a consistently greater incidence of autism compared to LBW boys [38].

Perinatal asphyxia and ASD have been linked in numerous studies, which lends credence to the theory that early brain injury may predispose to ASD [39-42]. A study comparing twins with ASD showed that across concordant and discordant twin pairs (i.e., if both or just one twin had ASD), signs of hypoxia, such as respiratory distress or having an oxygen need at birth, were all associated with an elevated risk of ASD. There are no birth asphyxia cases in our sample group, maybe because of the small number of cases.

Maimburg et al., through a study conducted at the UCLA-University of Utah epidemiologic survey of autism: prenatal, perinatal, and postnatal factors, found that an almost fourfold increased risk for infantile autism was observed in newborns exposed to hyperbilirubinemia (Maimburg et al. 2008). Neonatal jaundice is caused by accumulated bilirubin (mostly conjugated) physiologically or pathologically; it can, in the pathologic case, damage the central nervous system and result in bilirubin encephalopathy. Our study shows a consistent result of 32% (17).

Conclusion

Risk factors like a mother's blood group A, neonatal jaundice, and vitamin D deficiency are associated with developing autism in our study. This would assist policymakers in taking necessary steps to reduce the incidence of this disorder. The data is not strong enough to link the genesis of autism to other prenatal or neonatal events.

Conflict of interest.
Nil

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