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Risk Factors for Autism: A Comprehensive Summary

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Abstract

Objective: To review the evidence for the presence of etiological factors that affect the risk of autism and autism spectrum disorders.

Autism is a chronic neurodevelopmental disorder characterized by social and language impairments and stereotyped, repetitive patterns of behavior. Symptoms manifest by the age of 3 years, and affected individuals often require constant care from family members and professionals. Other disorders that are included in the autism spectrum include atypical autism, Asperger disorder, Rett disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified. The etiology of autism is unknown, although the risk factors based on pre-, peri-, neonatal and environmental exposures have been the focus of epidemiologic research for over 40 years. Current evidence suggests that several environmental factors are unrelated to risk of ASD. Birth complications that associated with trauma or ischemia and hypoxia have shown strong links to ASD, whereas other pregnancy-related factors such as maternal obesity, maternal diabetes, and C/S have shown a weak association with risk of ASD (Modabbernia & Velthorst et al, 2017).

In this study, systematic reviews and meta-analyses of risk factors for ASD were reviewed to provide an overview of the evidence of the presence of the risk factors of autism and autism spectrum disorder. Relevant articles were identified by searching the internet and 15 case histories eligible were reviewed for the study. The summary of the study reveals the presence of etiological factors of autism as reported by the articles, were present in the case histories studied.

Keywords: Autism, meta-analysis, etiological factors, autism spectrum disorders.

Introduction

Autism spectrum disorder (ASD) is a group of developmental disabilities characterized by impairments in social interaction and communication and restricted and repetitive interests/behaviors.

Autism was first reported by Kanner (1943) with a clinical description of 11 children showing “extreme aloneness from the very beginning of life, not responding to anything that comes to them from the outside world.” He proposed the behavioral combination of Autism, Obsessiveness, stereotypy, and Echolalia as Childhood Schizophrenia.

It is a chronic neurodevelopmental disorder, Social and language impairments and stereotyped, repetitive patterns of behaviour and symptoms manifest by the age of 3 years. According to DSM V, Autism spectrum disorder include Atypical autism, Asperger Disorder, Rett Disorder, Childhood Disintegrative disorder, and Pervasive Developmental Disorder Not Otherwise Specified.

Prevalence rates of both Autism and Autism Spectrum Disorders (ASDs) have greatly increased in the past decade.

In some children, signs of Autism can be seen early as 12 months. Babies that do not babble or point by age one could be showing early signs of Autism. Other children may develop normal language and social skills for a time, but then begin to regress as Autism presents. This is called Regressive Autism. Some people believe childhood vaccines cause older children to develop Autism, but this is not proven, and vaccinations should not be avoided.

Children with Autism may be sensitive to touch, certain smells, loud noises, temperature extremes, and even certain colors.

Overstimulation cause a child with Autism to become upset and have a meltdown. The child may be difficult to soothe and calm down. The reasons autism occurs are not understood, and researchers are looking for answers, as well as ways to prevent the disorder. Boys are more likely than girls to have autism.

Etiology

While in most cases of the exact etiology of ASD remains unknown, novel technologies and large population-based studies have provided new insight into the risk architecture of ASD and the possible role of environmental factors in etiology.
Various factors have been examined to understand the etiology and the risk factors of Autism.

Prenatal factors have been examined in various studies. The factors associated with Autism risk were advanced parental age at birth, maternal prenatal medication use, bleeding, gestational diabetes, being first born v. third or later, and having a mother born abroad.

The factors with the strongest evidence against a role in Autism risk included previous fetal loss and maternal hypertension, proteinuria, pre-eclampsia and swelling.

Birth complications that are associated with trauma or ischemia and hypoxia have also shown strong links to ASD, whereas other pregnancy-related factors such as maternal obesity, maternal diabetes, and caesarian section have shown a less strong (but significant) association with risk of ASD.

Evidence shows that perinatal hypoxia and hypercarbia are associated with various neurodevelopmental outcomes including seizure, cerebral palsy, and intellectual disability. A meta-analysis of ten studies by Chen et al. [2] found that maternal autoimmune disease is associated with a small but significant, precise, and consistent increase in risk of ASD in the offspring.

Many genetic conditions that are associated with ASD might also be associated with birth complications. Genetic mechanisms also serve to make the individuals susceptible to the effect of certain environmental risk factors. For example, many genetic conditions that are associated with ASD might also be associated with birth complications.

Jiang et al. systematically reviewed maternal infection during pregnancy and risk of ASD. Their most important findings include a small but significant increase in risk of ASD after maternal bacterial (18%) and genitourinary infection (9%). The risk was precise but inconsistent. They also found a small increase in ASD after maternal flu that was precise, inconsistent, and marginally significant.

The studies on toxic elements have been largely limited by their design, but there is enough evidence for the association between some heavy metals (most important inorganic mercury and lead) and ASD that warrants further investigation. Mechanisms of the association between environmental factors and ASD are debated but might include non-causative association, gene-related effect, oxidative stress, inflammation, hypoxia/ischemia, endocrine disruption, neurotransmitter alterations, and interference with signaling pathways. Over 60 perinatal and neonatal factors were examined in various studies. Over 50 prenatal factors have been examined in various studies. According to recent evidence, up to 40–50% of variance in Autism Spectrum Disorder liability might be determined by environmental factors.

The risk factors might be directly affecting of might be a significant factor that contribute to the presence of Autism and ASDs. We sought to systematically review the evidence for the presence of prenatal, perinatal, postnatal and environmental factors that affect the risk of Autism and ASDs.

Review of Literature

- Birth complications that are associated with trauma or ischemia and hypoxia have shown strong links to ASD.[1]

- Pregnancy-related factors such as maternal obesity, maternal diabetes, and Caesarean have shown a weak association with risk of ASD. [1]
- Factors associated were umbilical-cord complications, foetal distress, birth injury or trauma, multiple birth, maternal haemorrhage, summer birth, low birth weight, small for gestational age, congenital malformation, low 5-minute APGAR score, feeding difficulties, neonatal anaemia, Rh incompatibility, and hyperbilirubinemia. [6]
- The factors associated with Autism risk were advanced parental age at birth, maternal prenatal medication use, bleeding, gestational diabetes, being first born v. third or later, and having a mother born abroad. [3] Factors found by at least 2 studies and associated with at least a 50% increase in the risk of autism. [3]
- Increased risk factors included advanced maternal age, advanced paternal age, and place of birth. [10]
- Significant associations with pregnancy-induced hypertension, bleeding, caesarean delivery, congenital malformations, and daily smoking during pregnancy. [10]
- Evidence to suggest that parental age and obstetric conditions are associated with an increased risk of Autism and Autism Spectrum Disorders is accumulating. [10]
- Paternal age beyond 35 years was found to be significantly related to first trimester spontaneous miscarriages possibly causing autism and autism spectrum disorders. [12]
- Maternal diabetes was significantly associated with a greater risk of ASD in the offspring. [13]
- Type 2 diabetes, antidiabetic medication use was associated with higher ASD risk. [14]
- Children born to mothers who had metabolic conditions such as diabetes, hypertension, and obesity during pregnancy were more likely to have autism spectrum disorders. [15]
- Perinatal exposure to radiation is significantly associated with an increased risk of developmental disorders such as autism spectrum disorders (ASD) and attention-deficit hyperactivity disorder (ADHD). [16]
- Positive family history was found to be statistically significantly associated with the risk of autism. [17]
- High maternal age (mother, P35 years) at birth was found in 23% of autistic children. [17]
- Maternal PTSD symptoms were associated with 2–3 times greater risk of child's ASD. [18]
- Maternal-fetal incompatibility at the Rh or ABO loci may contribute to the risk of autism. [19]
- A connection was found between infection during pregnancy and the increased risk of autism in the offspring. [20]
- Maternal viral infection in the first trimester and maternal bacterial infection in the second trimester were found to be associated with diagnosis of ASDs in the offspring. [21]
- The prevalence of ASD, ADHD, and ID was higher among children born to mothers diagnosed with anemia within the first 30 weeks of pregnancy. [22]

- Mild to moderate hearing loss was diagnosed in 7.9% and unilateral hearing loss in 1.6% of those who could be tested appropriately. Hyperacusis was common, affecting 18.0% of the autism group and 0% in an age-matched nonautism comparison group. [23]
- Mild, fluctuating conductive hearing loss due to middle-ear anomalies may account for the language and attention problems of learning-disabled children . [24]

Need for Study

A fundamental question about the association between environmental risk factors, pre-natal, peri- natal and post- natal factors and ASD is whether the association represents an underlying causality or not and is associated with the possibility of the individual with ASD. A plausible explanation for many of the observed factors of ASD are reviewed in various research articles from various parts of the world under various categories and underlying actors. Furthermore, each factor might involve multiple mechanisms and at different levels of etiological pathways to ASD.

In the present paper, we conducted a review of systematic reviews and meta-analyses of the various risk factors for ASD. 15 case histories were reviewed in a single clinic setup to understand the presence of various risk factors present in the individuals diagnosed with ASD and the frequency of occurrence. For systematic reviews, we narratively summarized the authors' conclusion.

The aim of the study is to focus on the items listed below:

1. To understand the factors related to risk of ASD based on current evidences.

2. To understand the aetiology of autism better in Indian set-up.

3. To identify the risk factors that show strong link to ASD.

Aim

1) **To review the evidences**

An extensive study on the causes had been made to rule out the presence of etiological factors which showed strong links with ASD. 15 studies were reviewed where functional assessment served as the primary method of identifying the causes. Autism was previously reported to affect approximately 5 of every 10,000 children. 15 cases from our clinic have been taken to examine the risk of Autism and Autism Spectrum Disorders to check for the presence of etiological factors.

2) **Check for the presence of etiological factors**

We sought to systematically review the evidence for the presence of prenatal and perinatal factors that affect the risk of autism and ASDs. We have chosen to focus this review on studies that used large, population-based epidemiological samples to

explore associations between prenatal and perinatal variables and the risk of Autism and ASDs. 15 case histories were studied in detail to examine the factors such as pre-natal, peri -natal and post-natal conditions which had strong links to Autism and Autism spectrum disorders.

3) **To check for the risk of Autism and Autism Spectrum Disorders.**
We discuss the potential risk factors identified in this review and attempt to understand their etiological relevance and risk associated with Autism. Although not proven as independent risk factors for Autism, these variables should be examined in relation to the risk of Autism and Autism Spectrum Disorders.

METHOD

1) To review the risk factors of ASD

15 case histories from our clinic were included in our study to examine the potential risk associated with Autism and Autism Spectrum Disorders. From these case histories the pre-natal, peri-natal, post-natal and the environmental factors were reviewed. In pre-natal history factors, which were taken into consideration were miscarriage, use of medicines, infections, anemia, rh-incompatibility, diabetes, radiation and trauma. In peri-natal history factors which were taken into consideration were normal delivery, caesarean delivery, breach delivery, forceps delivery, precipitate delivery and prolonged delivery.

Under post-natal history factors which were taken into consideration were birth cry, hypoxia, cyanosis, jaundice, infection and convulsion. In environmental history factors which have been taken into consideration are family history, maternal smoking, vaccination and exposure to toxins.

2) Calculating mean

After reviewing the factors which showed strong links to ASD the mean was calculated by dividing the factors with the factors which were present.

Mean = no of factors affected - total number of factors present.

3) Systematic reviews

- Exposure to jaundice in neonates was associated with increased risk of disorders of psychological development for children born at term. [8]
- Strong association was found between Autism and the child suffering from jaundice. [8]
- Increased risk of Autism has been shown in neonates delivered by C-section. Risk of Autism associated with general anesthesia during cesarean delivery: a population-based birth-cohort analysis. [9]

- Two studies found a significant association between child delivered through c-section and Autism. [9]
- Low birth weight is considered a marker for newborns at high risk for Autism. [10]
- A causal association between CS and ASDs increase has been suggested. [11]

Procedure

15 case histories of participants diagnosed with Autism and Autism Spectrum Disorders. Routine diagnostic evaluations were carried out. The etiological factors are mentioned below.

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
1	Miscarriage	0	Normal	0	Birth weight	0	Family history	0	2
	Use of medicines	0	Caesarean	1	Birth cry	0	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	
	RH incompatibility	0	Precipitate	0	Jaundice	1	Consanguinity	0	
	Diabetes	0	Prolonged	0	Infection	0			
	Radiation	0	Premature	0	Convulsion	0			
	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
2	Miscarriage	0	Normal	0	Birth weight	0	Family history	0	1
	Use of medicines	0	Caesarean	0	Birth cry	0	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	
	RH incompatibility	0	Precipitate	0	Jaundice	0	Consanguinity	0	
	Diabetes	0	Prolonged	0	Infection	0			
	Radiation	0	Premature	0	Convulsion	1			

	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
3	Miscarriage	1	Normal	0	Birth weight	0	Family history	0	3
	Use of medicines	0	Caesarean	1	Birth cry	0	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	
	RH incompatibility	0	Precipitate	0	Jaundice	1	Consanguinity	0	
	Diabetes	0	Prolonged	0	Infection	0			
	Radiation	0	Premature	0	Convulsion				
	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
4	Miscarriage	0	Normal	0	Birth weight	0	Family history	0	3
	Use of medicines	0	Caesarean	0	Birth cry	0	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	
	RH incompatibility	0	Precipitate	0	Jaundice	1	Consanguinity	0	
	Diabetes	0	Prolonged	0	Infection	1			
	Radiation	0	Premature	0	Convulsion	1			
	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
5	Miscarriage	0	Normal	0	Birth weight	0	Family history	0	2
	Use of medicines	0	Caesarean	0	Birth cry	0	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	1	Vaccination	0	

	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	
	RH incompatibility	0	Precipitate	0	Jaundice	0	Consanguinity	0	
	Diabetes	0	Prolonged	0	Infection	0			
	Radiation	0	Premature	0	Convulsion	1			
	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
6	Miscarriage	0	Normal	0	Birth weight	0	Family history	0	2
	Use of medicines	1	Caesarean	0	Birth cry	0	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	
	RH incompatibility	0	Precipitate	0	Jaundice	1	Consanguinity	0	
	Diabetes	0	Prolonged	0	Infection	0			
	Radiation	0	Premature	0	Convulsion	0			
	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
7	Miscarriage	1	Normal	0	Birth weight	0	Family history	0	4
	Use of medicines	0	Caesarean	0	Birth cry	1	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	
	RH incompatibility	0	Precipitate	0	Jaundice	0	Consanguinity	1	
	Diabetes	0	Prolonged	0	Infection	0			
	Radiation	0	Premature	1	Convulsion	0			
	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
8	Miscarriage	0	Normal	0	Birth weight	0	Family history	1	3
	Use of medicines	0	Caesarean	0	Birth cry	0	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	
	RH incompatibility	0	Precipitate	0	Jaundice	1	Consanguinity	1	
	Diabetes	0	Prolonged	0	Infection	0			
	Radiation	0	Premature	0	Convulsion	0			
	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
9	Miscarriage	0	Normal	0	Birth weight	0	Family history	0	4
	Use of medicines	0	Caesarean	1	Birth cry	0	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	
	RH incompatibility	1	Precipitate	0	Jaundice	1	Consanguinity	0	
	Diabetes	0	Prolonged	0	Infection	0			
	Radiation	0	Premature	1	Convulsion				
	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
10	Miscarriage	0	Normal	0	Birth weight	0	Family history	1	6
	Use of medicines	1	Caesarean	1	Birth cry	0	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	

	RH incompatibility	0	Precipitate	0	Jaundice	1	Consanguinity	0	
	Diabetes	1	Prolonged	0	Infection	0			
	Radiation	0	Premature	0	Convulsion	1			
	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
11	Miscarriage	0	Normal	0	Birth weight	0	Family history	0	1
	Use of medicines	0	Caesarean	0	Birth cry	0	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	
	RH incompatibility	0	Precipitate	0	Jaundice	1	Consanguinity	0	
	Diabetes	0	Prolonged	0	Infection	0			
	Radiation	0	Premature	0	Convulsion	0			
	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
12	Miscarriage	0	Normal	0	Birth weight	0	Family history	1	2
	Use of medicines	0	Caesarean	0	Birth cry	0	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	
	RH incompatibility	0	Precipitate	0	Jaundice	0	Consanguinity	1	
	Diabetes	0	Prolonged	0	Infection	0			
	Radiation	0	Premature	0	Convulsion	0			
	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
13	Miscarriage	0	Normal	0	Birth weight	0	Family history	0	1
	Use of medicines	0	Caesarean	0	Birth cry	0	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	
	RH incompatibility	0	Precipitate	0	Jaundice	1	Consanguinity	0	
	Diabetes	0	Prolonged	0	Infection	0			
	Radiation	0	Premature	0	Convulsion	0			
	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
14	Miscarriage	0	Normal	0	Birth weight	0	Family history	1	2
	Use of medicines	0	Caesarean	0	Birth cry	0	Maternal smoking	0	
	Infections	0	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	0	Forceps	0	Cyanosis	0	Exposure to toxins	0	
	RH incompatibility	0	Precipitate	0	Jaundice	0	Consanguinity	1	
	Diabetes	0	Prolonged	0	Infection	0			
	Radiation	0	Premature	0	Convulsion	0			
	Trauma	0							

NAME	PRE-NATAL		PERI-NATAL		POST-NATAL		ENVIRONMENTAL		TOTAL
15	Miscarriage	0	Normal	0	Birth weight	0	Family history	1	6
	Use of medicines	0	Caesarean	0	Birth cry	0	Maternal smoking	0	
	Infections	1	Breech	0	Hypoxia	0	Vaccination	0	
	Anemia	1	Forceps	0	Cyanosis	0	Exposure to toxins	0	

	RH incompatibility	0	Precipitate	0	Jaundice	1	Consanguinity	0	
	Diabetes	1	Prolonged	0	Infection	1			
	Radiation	0	Premature	0	Convulsion	0			
	Trauma	0							

The number of factors present in the individuals are $^{42}/_{405}$.

Where the total number of factors present is 42

The total number of factors considered for the study is 405.

The MEAN of the factors present in the 15 individuals is 0.103 (the sum divided by the count).

- ✓ 6 out of 15 children had prenatal history.
- ✓ 5 out of 15 children had peri natal history.
- ✓ 13 out of 15 children had postnatal history.
- ✓ 6 out of 15 children had environmental history.

Number of prenatal factors present are $^{9}/_{120}$

Number of perinatal factors present are $^{6}/_{105}$

Number of postnatal factors present are $^{18}/_{105}$

Number of environmental factors present are $^{9}/_{75}$

Summary and Conclusion

- The summary of the study reveals the presence of aetiological factors of Autism as reported by the articles, were present in the case histories studied.
- There is insufficient evidence to implicate any factor in Autism aetiology, although there are some evidences to suggest that exposure to these risk factors based on pre-, peri-, neonatal and environmental exposures may increase the chances to lead to the complications of Autism and Autism spectrum disorders.

Limitations

- Not limited to one category of factors.
  The factors analysed in this study do not belong to only one category of factors. The articles chosen for the meta-analysis compromise of various factors explained across various locations with different no. of cases chosen for study.
  Not many articles were reviewed due to heterogeneity. The risk factors characterized in this review were evident across studies and present in the cases reviewed in the clinical study.

- Single clinic-based study.

To obtain basic understanding on the etiological factors and the association of the etiological factors with Autism and Autism Spectrum Disorders only a single clinical population of individuals diagnosed with Autism and Autism Spectrum Disorders according to DSM IV and DSM V were taken into consideration. The individuals belonged to a geographical location.

- Limited cases studied.
  Since the study was based on single clinic inconsistency of elaborate information and reliability were present in some results. This shows that it is especially important for future studies to use large, population-based data and accurate information to allow for precise and detailed assessments of the disorders and potential risk factors.

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