DOI: 10.7860/JCDR/2018/36431.11751

Review Article

Paediatrics Section

Autism Spectrum Disorders-Aetiopathogenesis

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ABSTRACT

Autism Spectrum Disorders (ASD) are characterised by a range of clinical features that can vary from individual to individual in both degree of severity and variability of the clinical presentation. The aetiology or causation of ASD has been a widely debated issue for several decades; however, the exact cause of autism is still unknown. Research has suggested that ASD may be caused by genetic and/or environmental factors. Among those, children with low genetic susceptibility, some maternal and obstetric factors have an independent role in autism aetiology, whereas among genetically susceptible children, these factors appear to play a lesser role. It was observed that there is an increased risk of ASD due to: (i) advanced maternal age; (ii) advanced paternal age; (iii) duration of gestation; (iv) intrapartum hypoxia; and (v) birth weight. Recent evidence also suggests potential links of immune dysfunction, dietary, metabolic and gastrointestinal factors.

Keywords: Environmental factors, Genetic factors

INTRODUCTION

Autism spectrum disorders are one of the most common neurodevelopmental disorders, with an estimated prevalence of 1-2% [1,2]. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), there were three separate names for ASD (Autistic Disorder, Asperger syndrome and PDD-NOS) but according to DSM-5, there is just one category: ASD. The major clinical features of autism are deficits in social communication and social interaction; and restricted, repetitive behaviours and interests [3]. The clinical features can vary from individual to individual in both degree of severity and variability of the clinical presentation. ASD is typically diagnosed on the basis of behavioural symptoms, without reference to aetiology. However, considerable research has been devoted to investigations of aetiological factors.

Aetiology, causation or causality, is the capacity of one variable to influence another. Causation is often confused with correlation, which indicates the extent to which two variables tend to increase or decrease in parallel. However, correlation by itself does not imply causation. On the other hand, a risk factor is any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury. The aetiology or causation of ASD has been a widely debated issue for several decades; however, the exact cause of autism is still unknown [4]. Research suggest that ASD may be caused by genetic and/or environmental factors [5]. Others have proposed that it may be a combination of three factors-genetic factors, prenatal, natal, postnatal developmental factors and environmental factors [6]. Till date, no study has conclusively proven the cause of ASD. Many have attempted to prove or disprove perceptions and hypotheses, but none have determined the exact aetiological factors. Here, we review the different aetiological factors in ASDs that have been described in the literature.

Genetic Factors

Even though autism is a multi-factorial disease, it has been proved that influence of various genes play a prime role in causation of the disease. Research findings have shown that genetic factors play an important role and empirical research has not been able to conclusively identify specific genes that cause ASD [7,8]. However, it may be of importance to try and understand the basic genetic research findings, even if it has little clinical relevance at present. It is reported that serotonergic dysfunction will cause neurodevelopmental abnormalities including autism and platelet hyper-serotoninemia as the prime endo-phenotype for the causation of autism. For example, among ASD children, it has been shown that there is: (i) a likely involvement of *ITGB3* gene and TPH2 in the causation of autism [9]; (ii) a significant increase in NF-kB binding activity in blood samples of children with autism [10]; (iii) higher frequency of MTHFR 677 T-allele (risk factor); (iv) lower frequencies of MTRR 66A allele and SHMT 1420T allele; and that (v) MTRR A66G and SHMT C1420T polymorphisms reduce risk for autism [11].

In the general population, Benayed R et al., observed a link between autism and *Engrailed-2 (EN2)* gene and this gene may contribute up to 40% of cases of autism. The authors suggest that mutation and disruption in the expression of *EN2* gene will cause ASDs, since the gene can alter the normal development of brain and other neural tissues [12]. In a 4-year-old male child with autism and facial dysmorphism, the genetic analysis demonstrated a micro-duplication of the 22q11.2 chromosomal region [13]. Neurodevelopmental impairment and behavioural problems are very common in patients with 22q11.2 duplication. Hence, it is proposed that genetic evaluation of ASD should include Fluorescence Insitu Hybridization (FISH) analysis of the 22q11.2 chromosomal region. The accumulating evidence suggests that the genetic architecture of autism resembles that of Intellectual Disability (ID), with many genetic and genomic disorders involved, each accounting for a small fraction of cases [14]. In fact, all the known genetic causes of ASDs are also causes of ID, indicating that these two neurodevelopmental disorders share common genetic bases.

Many genomic regions have been associated with aetiology of autistic behaviour, and it is estimated that all proposed regions together would be involved in the aetiology of less than 1% of cases. In addition, scientific evidence shows that changes in regions reported in ASD have also been described in other neuropsychiatric diseases, which suggests that there is an aetiological connection with phenotypes attributed to other neurodevelopmental abnormalities [15]. For example, some rare mutations associated with increased risk for ASD and schizophrenia have already been reported in 15q13.3, 16p11.2 and 22q11.21 and in the *NRXN1* gene [16]. A Swedish study reported that the existence of individuals with schizophrenia and bipolar disorder in the family is a risk factor for the occurrence of autism as the authors found an association between schizophrenic parents or siblings with increased risk of ASD. Bipolar disorder also

proved to be a risk factor, but not as strong as schizophrenia [17]. Studies of autistic families have also shown a significant increase in the recurrence of ASD in first-degree relatives of carriers. For example, siblings of individuals with ASD have a 22 to 25 fold higher risk of having the disorder [18]. There are significantly higher risk of ASD in offspring of parents with ASD and those with familial history of psychiatric problems. Depression and personality disorders have been reported to be more common in mothers of children diagnosed with ASD than in mothers of children with normal development [19]. Even some non-affected individuals of different generations in the same family may show subtle impairment in cognitive development, language changes or in social interaction and this is termed the broad autism phenotype. This phenotypic diversity of autistic behaviour and psychiatric manifestations in families of the patients indicate that the genetic factors that influence ASD may be composed of distinct elements that manifest differently between affected and non-affected family members [20]. A study from India revealed that consanguinity among parents increases the risk for ASD and this may be due to the genetic and environmental factors involved in the causation of autism [21]. In another study, it was observed that among those children with low genetic susceptibility, some maternal and obstetric factors had an independent role in autism aetiology, whereas among genetically susceptible children, these factors appeared to play a lesser role [22].

Antenatal, Natal and Postnatal Risk Factors

Many antenatal, natal and postnatal risk factors have been indicated as the causative factor for autism, which are mainly due to environmental toxins, infections and certain diseases occurring during pregnancy. Various epidemiological studies from the western world were reviewed and it was observed that there is an increased risk of ASD due to: (i) advanced maternal age; (ii) advanced paternal age; (iii) maternal place of birth outside Europe or North America; (iv) duration of gestation; (v) intrapartum hypoxia; and (vi) birth weight [23]. Studies with different methodology, but mostly case control design, have shown significant association of ASD in the baby with the following antenatal, natal and postnatal risk factors.

The significant antenatal risk factors in various studies were advanced maternal age, presence of antepartum haemorrhage, pregnancy induced hypertension, gestational age at birth less than 35 weeks, parental psychiatric history of affective disorders, maternal unhappy emotional state, high incidence of uterine bleeding, maternal vaginal infection, daily smoking in early pregnancy, maternal passive smoke exposure, later start of prenatal care, having a previous termination of pregnancy, increasing father's age, mothers aged >35 years, unwanted medication during pregnancy, maternal chronic or acute medical conditions, respiratory infections during pregnancy, gestational complications, oedema, abnormal gestational age (42 weeks), gravidity more than one, breech presentation, threatened abortion, lower gestation, maternal history of psoriasis, rheumatoid arthritis and celiac disease and family history of Type 1 diabetes [24-33].

The significant natal and immediate postnatal risk factors in various studies were caesarean delivery, foetal distress, preterm delivery, labour complications, low birth weight, small for gestational age, congenital malformations, neonatal jaundice, delayed birth cry, birth asphyxia, breech presentation, intra partum hypoxia, low Apgar score at five minutes, small for gestational age, male babies, multiple births, extreme preterm, not having/had breast milk, neonatal hypoglycaemia, respiratory distress, hyperbilirubinaemia after birth, new-born encephalopathy, abnormal cerebral ultrasound scanning results, abnormal neurological signs after birth, hyper tonicity and generalised hypo-perfusion of brain, as evidenced by Single Photon Emission Computed Tomography (SPECT) [34-38],

In a comprehensive meta-analysis done at University of Miami Miller School of Medicine, USA, it was observed that the factors associated with risk for autism were advanced parental age at birth, maternal prenatal medication use, bleeding, gestational diabetes, being first born versus third or later, and having a mother born abroad [33]. Reductions in risks of autistic disorders related to preterm birth may be primarily attributable to preeclampsia, small-for-gestational age birth, congenital malformations, low Apgar scores at five minutes, and intracranial bleeding, cerebral oedema, or seisures in the neonatal period. In a case control study of 143 confirmed cases of 2-6-year-old children with autism (CARS score of e"30), attending autism clinic of Child Development Centre, Kerala, India, the significant antenatal, natal and postnatal risk factors with statistically significant high odds ratios on multivariate analysis were: (i) excess foetal movement (OR=11.4); (ii) maternal respiratory infection/asthma (OR=6.1); (iii) maternal vaginal infection (OR=5.2); (iv) maternal hypothyroidism (OR=4.3); and (v) family history of neurodevelopmental disorders (OR=2.9)[39].

Socio-demographic Factors

The role of non-genetic factors other than biological factors also has to be highlighted, like the place of residence of the child, education of parents, Socio-economic Status (SES) and child rearing practices. Socio-demographic factors, particularly SES have been implicated as a risk factor for ASD. For example, in New Jersey, the prevalence of ASD is 17.2 cases per 1000 children in homes with average income above $90,000 and only 7.1 cases per 1000 children in homes with median income less than $30,000 [40]. This may not be due to a protective effect of lower SES. It may be due to under diagnosis, lack of surveillance by physician/parent/teachers and reduced access to services. For many chronic childhood disorders and developmental disabilities, the association with SES often is found to be inverse, such that population prevalence decreases with increasing levels of SES [41].

The risk of autism was shown to be associated with increasing degree of urbanisation of the child's place of birth and with increasing paternal, but not maternal age [42]. Children of men 40 years or older were 5.75 times more likely to have autism compared with offspring of men younger than 30 years [43]. The risk of infantile autism was increased for mothers: (i) aged more than 35 years; (ii) with foreign citizenship; (iii) those who used medicine during pregnancy; (iv) children with low birth weight; and (vi) children with congenital malformations [37]. In a case control study of 143 confirmed cases of two to six-year-old children with autism (CARS score of e"30), attending autism clinic of Child Development Centre, Kerala, India, the significant socio-demographic risk factors with statistically significant high odds ratios on multivariate analysis were: (i) upper and upper middle SES (OR: 7.1); and (ii) male gender (OR: 3.9), whereas place of residence, rural (OR: 0.41) was a protective factor [44].

Nutritional/ Environmental factors and Child Rearing Practices

Nutritional factors: Gastrointestinal disorders are commonly seen in autistic children and the common symptoms include chronic constipation, diarrhea and abdominal pain. Chronic dueodenitis and reflux oesophagitis has been seen in up to two-third of autistic children [45]. Most of the children have a form of inflammatory bowel disease and some have food intolerance and sensitivity to food proteins including lacto globulin and case in [46]. A review article published on the gluten-free, casein-free diet in autism, indicated that the prevalence of ASD appears to be on the rise, and there exist no clear aetiology or cure [47].

It has also been suggested that autism is an emotional disturbance due to disturbance in the opiate systems in the brain [48]. The opioid peptides (exorphins) are derived in the body from partially digested protein from the food and a study from Norway reported that the mean level of exorphins was about two times high in autistic when

compared to normal children [49]. It has been postulated that the exorphins were formed from casein (milk proteins) and gluten (wheat proteins) and this protein cross the blood-brain barrier and cause the symptoms of the disease, forming justification for proposing Casein Free and Gluten Free (CFGF) diet [50]. Out of desperation, many families are turning to new therapies and interventions provided in various media sources and anecdotal reports from other parents. Unfortunately, many of these newer, well publicised interventions have little empirical support.

It has been suggested that fatty acid deficiencies or imbalances may cause neurodevelopmental disorders in children. Nutritional abnormalities are commonly seen among ASD children. For example, they have significantly lower plasma levels of omega-3, fatty acids than controls, and their serum vitamin-D levels are significantly less [51,52]. A randomised, double-blind study done to find out the effects of 1.5 g/dL of omega-3 fatty acids (Eicosapentaenoic acid-EPA, Docosahexaenoic acid-DHA) supplementation in children with autistic disorders having severe tantrums, aggression, or self-injurious behaviours, revealed that omega-3 fatty acids have superiority over placebo in improving the symptoms [53]. However, in a study done on behavioural effects of omega-3 fatty acid supplementation in young adults with severe autism, who received two fish oil capsules per day containing Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) for six weeks, no significant improvements were observed with regard to the severity and frequency of problematic behaviours either during the active treatment period or during the six week observation period and on the number of episodes [54]. In a case with childhood disintegrative disorder, it was revealed that the child had vitamin-B12 deficiency and hyper-homocysteinemia, suggesting the need for detailed evaluation of all such cases having regression of neurodevelopment, since Vitamin-B12 deficiency if present, can be treated [55].

Environmental factors: There is an increasing perception and some evidence that deteriorating environmental conditions and many of the environment toxins, pollutants, food adulterations and thimerosal in vaccines are the culprits for the causation of autism. Lead, methyl mercury, polychlorinated biphenyls, arsenic, toluene, manganese, DDT, fluoride, ethanol are some of the environmental toxins that are probably involved. Electromagnetic radiation from cell phones, cell towers, Wi-Fi devices, microbial toxins, etc., are indicated as risk factors for autism. However, review of literature does not give much convincing evidence. It was proposed that autism may be caused by mercury. However, several epidemiological studies failed to find a correlation between mercury exposure through thimerosal, a preservative used in vaccines, and the risk of autism. Recently, it was found that autistic children had a higher mercury exposure during pregnancy due to maternal dental amalgam and thimerosal containing immunoglobulin shots. It was hypothesised that children with autism have a decreased detoxification capacity due to genetic polymorphism. It has been observed that repetitive doses of thimerosal lead to neurobehavioural deteriorations in autoimmune susceptible mice. Promising treatments of autism involve detoxification of mercury, and supplementation of deficient metabolites [56].

Thimerosal in vaccines: The connection between Measles, Mumps, and Rubella (MMR) vaccine and autism is based on two theories. One is based on the fact that some fraction of the vaccine will cause enteropathy due to mal-absorption which will cause absorption of toxic neuro-peptides into brain causing autism. The other theory involves the role of a preservative used in vaccines the thimerosal, a combination of ethyl mercury and thiosalicylate. There have been many legal battles in USA with regard to claims filed for compensation by parents of autistic children [57]. It has been proved beyond reasonable doubt that MMR vaccine is not a causative factor for autism. In a study done at Denmark from 1991 to 1998 among 537,303 children, it has been disproved that MMR vaccination causes autism [58]. The research studies done by Geier DA and Geier MR, had postulated that there could be an association between thimerosal and autism [59], but further studies in this direction have refuted the association between thimerosal and autism [60]. In a sound epidemiological study done at Department of Psychiatry, Montreal, it was proved that there is no association between ASD and immunising the child with measles or MMR vaccine [61].

Contrary to the perception of parents and family members, there has been no scientific proof that vaccines are linked to ASD [62]. Gerber JS et al., summarised several studies conducted in various parts of the world and have shown no correlation between the vaccine and autism [63]. A recent study also has confirmed that there is no relationship between vaccines and ASD, even among children who are genetically predisposed [64]. In summary, it may be stated that, although the number of autistic children has increased over the last decade [65], on the basis of current evidence, it is not possible to infer that thimerosal and autism are linked.

Poor child rearing practices: Developmental research has shown that the home environment may serve as a protective factor for children [66]. It is suggested that early social environment plays a role in mediating establishment of neural networks that regulate a child's response to stress and capacity for self-control [67]. Healthy brain development depends upon the care and support provided by individuals in the community as well as in the family. Home environment scores were found to be significantly related to mental development, independent of parental education and occupation [68]. Healthy brain development depend upon the care and support provided by individuals in the community as well as in the family [69]. Home environment scores are found to be significantly related to mental development, independent of parental education and occupation. The quality of mother infant interaction and the presence of age appropriate play materials may be used as a surrogate for the evaluation of quantity and quality of stimulation available at home. This then calls for a fresh look at the home care, stimulation and psychological environment of the child. In a case control study of 143 confirmed cases of 2-6 years old children with autism (CARS score of e"30), attending autism clinic of Child Development Centre, reveled the following risk factors as significant (i) child does not play with children of same age (OR=19.6); (ii) no outings (OR=3.4); (iii) do not tell stories/sing songs to the child (OR=3.2); and (iv) breastfeeding duration nil/ <6 mo (OR=3.4) [44].

Other factors: There are numerous hypotheses regarding the aetiology and pathology of ASD, including a suggested role for immune dysfunction. Immune abnormalities were first described in individuals with ASD in 1977 [70]. Proteomic analysis indicates that the levels of many immune proteins in plasma/sera, such as cytokines, chemokines, complement proteins, adhesion molecules and growth factors are altered in ASD [71]. However, to date, the evidence for involvement of the immune system in autism has been inconclusive. While immune system abnormalities have been reported in children with autistic disorder, there is little consensus regarding the nature of these differences which include both enhanced autoimmunity and reduced immune function [72].

Recent evidence suggests potential links between dietary, metabolic, infective, and gastrointestinal factors and the behavioural exacerbations and remissions of ASDs. Many studies pointed out that Gastrointestinal (GI) symptoms are prominent in ASD individuals. Wang LW et al., found more GI syndromes, including constipation (20%) and diarrhea (19%), in children with ASD than in their unaffected siblings (42 vs. 23%, respectively) [73]. It was also observed that patients with ASD who present GI symptoms might display significant behavioural manifestations, such as anxiety, self-injury and aggression [74]. Accumulating evidence also demonstrates that the gut microbiota is directly or indirectly associated with ASD symptoms, in part by influencing the immune system and metabolism [75].

CONCLUSION

Autism spectrum disorders are characterised by a range of clinical features that can vary from individual to individual in both the degree of severity and variability of the clinical presentation. The aetiology or causation of ASD has been a widely debated issue for several decades; however, the exact cause of autism is still unknown. Research has suggested that ASD may be caused by genetic and/or environmental factors. Among those children with low genetic susceptibility, some maternal and obstetric factors have an independent role in autism aetiology, whereas among genetically susceptible children, these factors appear to play a lesser role. Excess fetal movement, maternal respiratory infection/asthma, maternal vaginal infection, maternal hypothyroidism and family history of neurodevelopmental disorders are possible antenatal, natal and postnatal risk factors for autism. Upper and upper middle SES and male gender are significant socio-demographic risk factors for autism, whereas place of residence, rural is a protective factor. Early child care practices at home, specifically breastfeeding duration nil/<6 months, child does not play with children of same age, do not tell stories/sing songs to the child and no outings for the child are also definite risk factors for autism.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Mar 15, 2018**
Date of Peer Review: **Apr 03, 2018**
Date of Acceptance: **May 30, 2018**
Date of Publishing: **Jul 01, 2018**