

Autism Spectrum Disorders - A Review on The Preventive Aspects

Smitabh Barik¹, Lipilekha Patnaik^{2*}, Sumitra Pattanaik³

^{1,2,3}IMS & SUM Hospital, Siksha 'O'Anusandhan deemed to be University, Bhubaneswar, India

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ABSTRACT

Autism Spectrum disorder (ASD) is a neurodevelopmental disorder presenting with defects in social communication skills and repetitive sensory motor behaviour. There has been increasing concern regarding this disorder due to its increase in incidence and prevalence in recent years. Since it stays for lifelong and has no specific pharmacological treatment, many studies are being conducted to find ways of preventing this disorder. Better understanding of the causative factors will lead to better development of prevention strategies. This review aims at highlighting the methods of prevention of ASD which are mostly focussed on the environmental factors causing ASD as well as the ongoing researches on development of drugs and genetic modification using animal models. Some studies have shown preventive effects of factors such as nutrition supplements such as Vitamin D and folate, breastfeeding and avoiding exposure to harmful chemicals and drugs. The aim is to prevent the occurrence of the disorder and preventing the severity of symptoms wherever possible. Still more studies are needed to establish the exact association between the possible causative factors and ASD so that clinical trials can be done to establish the preventive effects in future.

Key words: ASD, risk factors of ASD, early intervention in ASD

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***Correspondence:** Dr. Lipilekha Patnaik (Email: drlipilekha@yahoo.co.in)

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INTRODUCTION

Autism spectrum disorders (ASD) constitute a diverse group of neurodevelopmental disorders which comprise of a constellation of deficits in social communication as well as repetitive sensory-motor behavior.^{1,2} In the Diagnostic and Statistical Manual of Mental Disorders (DSM), ASD is presented as a behavioural diagnosis describing a constellation of social communication impairments and repetitive restrictive behaviours which may occur in a context of a number of biological conditions.^{3,4} These disorders are complex, pervasive and multifactorial⁵ and highly heritable.⁶

In the last 50 years, ASD was narrowly defined and considered as a rare disorder of childhood onset as compared to recent times, when it is very well researched, publicized and recognized as a more common heterogenous disorder.^{7,8}

Autism word is derived from the Greek word "auto" meaning 'self'.⁹ It was first described by Leo Kanner in 1943^{10,11} and thought to be a rare disorder. Earlier the term autism spectrum disorder constituted multiple distinct disorders such as Autistic disorder, Asperger disorder, Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS). Now in the Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (DSM-5) all these disorders are together combined as autism spectrum disorders.^{2,12}

ETIOPATHOGENESIS

The exact etiopathogenesis of ASD still remains uncertain.¹³ There are various hypotheses regarding the causation, with the most accepted hypothesis being the interplay of genetic, epigenetic and environmental factors.^{9,14,15} Genetics plays a major role along with environmental factors which contribute to a lesser extent.¹⁶ Epigenetic factors are molecular mechanisms that alter gene expression by chemical modification on DNA without affecting the genome sequence¹⁷ such as DNA methylation and microRNA alterations.¹⁸ These genetic and environmental factors cause imbalance of neurotransmitters, abnormal neuronal pathways and abnormal neuronal connectivity and synaptogenesis.

DIAGNOSIS AND TREATMENT

Diagnosis can be made as early as 18-24 months of age, as at this age the characteristic symptoms of ASD can be differentiated from those appearing due to developmental delay or other delays.^{19,20} The diagnosis is difficult²¹ and made on the basis of behaviour and there are no reliable biomarkers for diagnosis of this condition.²² The diagnostic criteria are based on two domains of function, which are¹ Deficit in social communication and² Repetitive behaviour and restricted interests.^{10,23,24} Along with this a detailed

birth history, parental history, drug history, developmental history, and history of any psychiatric disorders in the family should be taken. Detailed clinical observation and review of data from care providers and/or teachers should be taken.

The mainstay of treatment is based on education and behavioural therapy with medications as an adjunct²⁵ Till date no specific pharmacological medication has been approved by the FDA. Many complementary treatments such as dietary modifications, vitamins, chelation, immunologic agents etc are also being used.

PREVENTION OF ASD

Need for prevention - Preventive strategies seem to be very logical as these can be cost effective considering the high financial cost for treatment of ASD. Also, there are non-availability of any specific drug for the treatment of ASD.²⁶ The etiological factors associated with ASD are genetic, epigenetic and environmental as well as an interplay of the above factors. Out of these, as a preventive measure, we can deal with the environmental factors to a large extent in order to decrease their causative effect on ASD.

Levels of prevention

Three forms of prevention can be implemented in case of ASD.²⁷

- 1) Primary prevention: This will help to reduce the incidence of this disorder.
- 2) Secondary prevention: This will help to reduce the disease severity.
- 3) Tertiary prevention: This will focus on preserving the functional adaptation and well-being of the affected subjects.²⁸

Prevention strategies

Prevention strategies need to be applied in a life course manner starting from the prenatal period up to old age. Focus can be made on the various types of prevention depending on the age of the subject.

Maternal factors- Age during conception, maternal infections, maternal stress and emotional condition, use of certain high-risk medications, obesity, smoking,^{29,30} detection of gestational diabetes and other metabolic conditions.^{31,32,33} Advanced maternal age (≥ 40 years) has been seen to be associated with development of autism in the child.^{34,35} Along with this advanced paternal age (≥ 50 years) is also a risk factor for development of ASD.^{34,36,37} Proper premarital counselling and increasing awareness among the general population regarding the effect of parental age at conception can help to somewhat reduce the incidence of ASD. Maternal infections such as rubella, influenza and other bacterial and viral infections can be prevented by stressing upon strict immunization coverage along with appropriate therapeutic measures.^{38,39} Maternal stress, depression, other

emotional conditions have significant negative effect on fetal development. These factors increase the production of maternal cortisol and also increase the permeability of the placenta to adrenal steroids.⁴⁰ This needs to be prevented by stress management and if needed help from the medical experts such as psychiatrists and psychologists should be sought. Several medications during pregnancy have been implicated as risk factors for ASD in the developing fetus. These are antiepileptics⁴¹ such as valproate, anti-asthmatic β -2 adrenergic receptor agonists⁴², selective serotonin reuptake inhibitors (SSRIs) etc., so these medications should be substituted or if possible, avoided during pregnancy.^{43,44,45}

IMPORTANCE OF MATERNAL NUTRITION

Maternal nutrition in the perinatal period plays a fundamental role in etiopathogenesis of ASD.⁴⁶ Deficiency of certain nutrients such as folic acid, vitamin-D and certain fatty acids can augment the development of ASD.⁴⁰ Correction of nutrient deficiencies need to be done for vit-D, Polyunsaturated fatty acids such as Omega-3 fatty acid as well folic acid. A prospective study in siblings of proband showed that supplementation of vitamin D during pregnancy or to infants led to a four-fold reduction in recurrence.⁴⁷

Importance of vitamin-D supplementation: Vit-D is a neuro steroid that helps in brain development through cellular proliferation, calcium signaling, neurotrophic and neuroprotective effects. Researchers in China have found that women with very low levels of Vit-D had a fourfold risk of having a subsequent autistic child.⁴⁸ There is good amount of evidence suggesting deficiency of Vitamin-D during gestation and early childhood may cause autism in some cases.^{49,50,51} Studies showed that children having lower Vit-D levels at 3 months of gestation, at birth and at 8 years of age were more likely to become autistic.^{48,52} Also, another study in Egypt found inverse correlation of serum Vit-D levels and the severity of ASD. The male predominance of autism is also associated with Vit-D levels as studies showed that testosterone inhibits the gene that activates Vit-D whereas estrogen enhances the beneficial effects of Vit-D on the brain.⁵³

In a recent study it was seen that polymorphisms of genes coding Vit-D receptors were also strongly associated with ASD. All the children having low Vit-D levels do not get ASD, genetic predisposition is still needed.⁵⁴

Since there are very few primary and secondary prevention intervention trials, the association between Vit-D and ASD is difficult to determine unless more randomized placebo control trials of Vit-D as a preventable measure are reported. But there is growing evidence for the association between the above two.

In contrary, many studies did not find any difference in the concentration of Vit-D among mothers of chil-

dren with and without ASD.⁵⁵ One study reported fourfold decrease in the recurrence rate of autism in newborn siblings when Vit-D supplementation was given during pregnancy.⁴⁷

It was hypothesized that high doses of Vit-D would improve the symptoms of some autistic children. Clinical trials have shown that high dose of Vit-D during gestation, infancy and early childhood may prevent most of ASD. Recent study on rat model of ASD reported that Vit-D had significant protective as well as treatment effect.⁵⁶ In a meta-analysis on Vit-D levels in ASD it was concluded that autistic children with reduced Vit-D level may have clinical consequences and therefore Vit-D levels in all autistic children should be checked and if low, should be given supplementation.⁵⁷ According to Mazahery et al all practitioners should consider Vit-D as a preventive and treatment measure for ASD.⁵⁵

Role of Folic acid: Folate deficiency during early pregnancy may interfere with DNA methylation leading to disruption of proliferation and migration of neural progenitor cells resulting in ASD associated brain abnormalities.⁵⁸ Children with autism show higher serum levels of homocysteine which may be due to decreased folate intake.

Studies have shown contribution of folic acid supplementation in pregnancy as well as blood folate levels of children for developing autism.^{59,60} Folic acid supplementation in autistic children have shown normalization of folate levels and relieve the symptoms of ASD. There are very few and contradictory studies with inconsistent conclusions regarding the effect of folic acid supplementation in pregnancy and development of autism in the subsequent child.⁶¹

Many studies have demonstrated the effect of maternal folic acid supplementation in decreasing the risk of ASD in the offspring.^{62,63} A meta-analysis done in China regarding effect of prenatal folic acid supplementation and offspring's autism spectrum disorder showed that maternal folic acid supplement given during the prenatal period had lower (43%) odds of ASD development in the offspring as compared to the subjects not receiving the supplementation.⁵⁸

EFFECT OF VIRAL INFECTIONS DURING PREGNANCY

Studies have shown that maternal viral infections during critical in-utero neurodevelopmental period may lead to increased risk of autism. The mechanisms can be direct teratogenic effect or indirect immunological and inflammation related effects on the developing brain.

Viruses such as Rubella, Measles, Mumps, Cytomegalovirus, Polyomavirus and influenza virus have shown to be linked with risk of developing autism in the offspring.⁶⁴ Proper immunization coverage should be stressed upon to prevent occurrence of

these infections. Early screening and detection of viral infection may prevent the development of ASD. This knowledge can help establish preventive measures for ASD in future.

BENEFITS OF BREASTFEEDING

Breastfeeding serves as a putative protective factor for ASD. Though the exact mechanism is unclear, many theories explaining the mechanism of effect of breastfeeding on autism are- Nutrition theory, Oxytocin stimulation and secretion of specific neurotrophic factors in the breast milk.⁶⁵ Results of few studies suggest that breastfeeding may confer a protective role related to the risk of developing autism.⁶⁵

Also, Insulin like growth factor (IGF) deficiency dysregulates myelination and is thought to be pertinent to the pathophysiology of ASD.⁶⁶ Breastmilk contains good levels of IGF and thus might reduce the risk of ASD.

ENVIRONMENTAL FACTORS

These include exposure to chemical pollutants which include pesticides⁶⁷, plastics, fragrances, air pollution. These can cause endocrine disruption and hence prevention of these factors at a community level can help reduce the exposure.

Studies have found higher concentration of heavy metals like lead, mercury and cadmium in hair of Autistic children as compared to normal children. Also, some studies show high concentrations of lithium, molybdenum and selenium. These chemicals are neurotoxic and are clearly associated with occurrence of Autism.⁶⁸ There comes the role of the society and the governing authorities to check heavy metal pollution and prevent poisoning.

INTERVENTION IN FIRST THREE YEARS OF LIFE

Most impairment occurs at this age as the child develops inability to pay attention to and integrate with social stimuli.⁶⁹ Studies have shown that ASD children can be more evidently differentiated from normal developing children at 12 months of age. For earlier diagnosis developmental regression may be used or by observation of clinical "red flags".⁷⁰ Earlier the detection earlier can be the preventive interventions.

Habitual eating behaviour or aversions for certain food causes nutrient deficiencies such as vitamins, minerals and fatty acids which worsen the symptoms in these children.⁴⁰ It is challenging to feed these children with optimum nutrients because of picky eating habits, food refusal and selectivity. So, supplements should be used in order to prevent deficiencies of multivitamins and micronutrients.

Nutritional intervention strategies have been explored such as – Gluten free casein free diet,^{71,72,73} Ketogenic diet,⁷⁴ Antioxidant diet, Iron diet, Fatty acid and Vitamin D supplementation.⁴⁰ Ketogenic diet has shown to be associated with improvement in social behaviour.

These children may have food sensitivities and they are intolerant to some food items. The mechanism behind this is inflammatory cytokines produced which incite immune reactions.⁴⁰

Gut microbiota are specific population of microorganisms present in the intestine which provide several beneficial effects by defending from pathogens, producing nutrients such as vitamins and promoting the immune system. Gut microbiota has a role to play in neurodevelopment as they stimulate GI tract to produce neurotransmitters and hormones which affects the central nervous system through the gut-brain axis.⁷⁵

Thus, using probiotics such as lactobacilli and saccharomyces significantly influence the gut microbiota composition and studies have shown that it can be an effective treatment for symptoms of ASD.⁴⁰

PIK3-AKT/ mTOR signalling pathway is involved in different neuronal functions by synaptogenesis and corticogenesis.⁷⁶ Upregulation of this pathway leads to axonal dysregulation and neuronal circuit connectivity which regulate certain cellular processes and features of ASD.⁷⁷ Inhibition of this pathway can give beneficial outcome by prevention of symptomatology, though complete inhibition has many side effects such as hyperglycaemia, hypertriglyceridemia etc.⁷⁸

There are many well described preventive interventions such as Paediatric autism Communication Therapy (PACT) and Early Onset Denver Model (ESDM).^{79,80} PACT is based on use of parent-child interaction and play and aims to improve social communication skills along with decreasing the restrictive repetitive behaviours. The therapy comprises 6 months of one and half hour fortnightly sessions and monthly sessions for next 6 months. ESDM aims to develop social communication skills, play skills, development of relationships and language and interest in others. It also uses child-tailored programs and activities for skill development. Progress of the child is reviewed every 3 months.⁷⁹

These studies have shown that secondary prevention is feasible, cost effective and can reduce the prevalence of ASD. Different programs can be combined on a personalised basis with an aim to develop a child's social interest, learning in natural settings, developing communication skills and enrichment of his/her responses.

Dawson and colleagues have proposed a developmental model comprising of the risk, processes, emergence of symptoms and adaptation in order to understand early brain plasticity and its role in prevention of this disorder. Understanding this model, prevention can be implemented by designing treat-

ments to alter the course of early behavioural and brain development in at risk infants.⁶⁹

According to this model the genetic, environmental, and phenotypic risk indices will help in very early identification of infants vulnerable to develop ASD. The altered interaction between genetic and environmental factors are hypothesised to cause complex social brain circuits leading to abnormalities in normal social and linguistic brain development.⁶⁹

CHILDHOOD AND ADULTHOOD

Supportive as well as therapeutic measures at this period will improve the overall quality of life and prevent detrimental consequences in the future which may be caused by the current difficulties. Both the family members and the school or any other institution has important role to play for providing proper environment in order to attain a major future effect. Majority of interventions are applied in the pre-school or the school going children. The strengths and weaknesses of each subject should be understood in order to make short and long-term goals. There should be focus on development of social and communication skills by intensive behavioural interventions or targeted interventions such as speech and language. Many programs and interventions are there for such skill development such as - Naturalistic Developmental Behavioural Intervention (NDBI), Social communications/ emotional regulation/ transactional support (SCERTS), Social skills programs such as Program for the Education and Enrichment of Relationship Skills-PEERS, can prevent isolation of individuals and improve quality of life.⁷⁹

A meticulous screening for comorbid medical and psychiatric conditions should be done as these conditions can have very detrimental effects if missed. If such comorbid conditions are noticed, interventions like psychopharmacology or cognitive behavioural therapy should be used.

FUTURE PREVENTION STRATEGIES

Now many researches are being conducted on animal models on the ways to prevent ASD. Genetic mouse models have been studied by genetic manipulations and non-genetic mouse models studied by use of infection or inflammation induced ASD and then attempts have been made to ameliorate and prevent ASD like symptoms. Valproic acid induced ASD mice models have shown successful effects to antioxidants (astaxanthin, green tea and piperine) and S-Adenosylmethionine (SAM). However, very rarely complete prevention was achieved.

There are very few data available on attempts of translation of animal model ASD to human ASD. If explored further, they can be beneficial in prevention

of ASD in future if appropriate clinical trials can be conducted.⁸¹

CONCLUSION

The incidence and prevalence of autism spectrum disorders are on an increasing trend. There is yet a lot to understand about the exact etiology and pathophysiology of this disorder. With no specific pharmacological treatment, it becomes more difficult to manage cases as each case is different from the other and needs personalised management. This causes a large amount of financial burden to the caretakers. More understanding of the etiological factors has led to more studies regarding preventive aspects of autism spectrum disorders. Many environmental factors are targeted which can be modified to prevent this disorder. These include prevention in the pre and perinatal period such as prevention of exposure to harmful chemicals and drugs, early detection and treatment of maternal infections, nutritional supplementation in the mothers during pregnancy and breastfeeding and adding nutrient supplements in infancy. Along with this, interventions can be done in the early childhood to prevent severity of symptoms.

Nowadays there are ongoing studies on animal models with an aim to modify the genetic risk factors and thus help to prevent autism in the future. More studies in future may help emergence of more cost-effective ways of prevention of ASD and thus decrease the burden.

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