Review article:

Autism: A review

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Abstract

Childhood milestonesneed meticulous tracking; any peculiar behavior needs immediate attention. There are large number of mental disorders seen in children;among them anxiety, depression, hyperactivity etc. are most frequent. The Autism Spectrum Disorder (ASD) is one of the prevalent and complex psychological ailments. Even though its incidenceis increasing; often itremainsunrecognized. Such individualsneedearly recognition and attention. Theirattendants should be educated for life-long hassle free care of ASD individuals. Research in this direction has progressed by leaps and bounds; but literature in this field is most complex and eludes consensus. This review on ASD is addressing the gist of outcome of researchfindings. Authors intend this presentation to have comprehensive understanding of ASD for family physicians and general readers.

Key words: Autism,Denovo, Epigenetic

Introduction:

Personality of every individual is a product of biology of brain. Its development, growth and maturity play an important role in one's lifespan.Every Person and his personality is an outcome of his perceptionof his or her surrounding environment throughout life.The basic anatomical pattern of the human brain is similar but functionally it forms a unique entity because of variable genetic, familial, and socialenvironment. Often we noticeatypical personalities in our society; their behavior, attitude, communication skill, response show some remarkable difference.Suchindividuals are initially identified by their parents, care takers; teachers etc. who are having close interaction with them throughout thechildhood. Autism is one such entitywhich encompasses the group of disorders that categorizes the personalities based on type and severity of its presentation.Recent global estimation quotes about 52 million autism cases worldwide[1]. Theincidence of autism has sharply increased during recent years to a record level worldwide.The medical science has contemplated extensively and in depth to understand about the brain and behavior through neurobiological studies.Such people need to be identified early and measures to be taken to improve their quality of life.

What is Autism?

Autism is a prototypic pervasive developmental disorder (PDD) typically exhibit subnormal social interactions, reduced language proficiency, and as well as diminished movements, general and social interests[2]. Affected individuals are exhibiting stereotypical behavior which starts generally before 3rd year.Pervasive developmental disorders are most atypical in their presentation andcan be recognized during the early childhood. It is often inevitable for the parents and care takers to pediatricians, psychiatrists, psychologist, neurologists' etc. for initial problems exhibited by the child. Some minor complaints like overt and aggressive behavior can be treated with pharmacological interventions. In

addition they may seek the help of non-pharmacological interventions by behavioral therapist, speech therapist, councilor, sports therapist, yoga therapist etc. for the betterment of autistic patients[3].

Historicalaspects: The history of autism stands almost 60 years old. The two pioneers Kenner from USA and Asperger from Austria have described about early autistic disorders in their thesis.Kenner has described about early autism as "autistic disturbances of affective contact" and in the subsequent years Hans Asperger has mentioned similar findings in his thesis as "autistic psychopathy in childhood". Both the scholars have used a common term "autistic" it was initially coined by Bleuler, a Swiss psychiatrist. Leo Kenner is considered to be a pioneer in the field of autism research[4,5].

Etiology: There are multiple factors including genetic susceptibility to environmental factors which threaten during pre and postnatal life.Host and environmental interplay also stands as an important factor inducing disease manifestation.Etiology of ASD is one of extensively debated topic since decades. The exposure to xenobiotics is considered to be one of the great threats affecting the bio system. The aluminum (Al) used widely in vaccines is considered as a risk factor. Adjuvants are the components associated with vaccines which potentiate the immune response to an antigen. They are generally used to augment the effect of vaccine by stimulating the immune system. But several studies in this regard couldn't reach any clear co-relation between use of such vaccines and incidences of ASD[6].

Epidemiology: ASD prevalence is4 to 5 per 10,000 children under 16 years of ageworldwide[7]. There may be several confounding factors involved in data, but statistically proven increase in the incidence of autism could be due to increase in awareness regarding disease entity, and also due to properly recorded diagnosis of the patient.Before 1970s autism was not clinically recognized distinctly. After 1980sincreasing awareness of role of chromosomal disorders in the disease process was identified and used for classification and distinction of ASD. Recent understanding about this ailment is a result of exclusive attention it has received in past 30 years[8].

Types: Ongoing research in the ASD study revealed more subtypes of ASD by considering variable clinical and cytogeneticfindings. Phenotype and behavior analysis of ASD may show some similar clinical expressions despite subtle difference in their genetic profile. For our understanding, autistic spectrum disorders are considered under following groups, despite their presentations showing overlapping characters, i.e. Autism disorder, Asperger disorder, Pervasive developmental disease-not otherwise specified, Rett's disorder, Childhood disintegrative disorder[9].

These classifications are showing narrow margin to differentiate them clinically, genetically about 10% of ASD hold good and some may remain inconclusive.

Autism Disorder-A widespread disorder characterized by abnormal social interactions and communications.

Asperger Disorder-Characterized by difficulty in social interactions and nonverbal communications with restricted and repetitive behavior.

Pervasive Developmental Disorder-not otherwise specified–There is delay in development of multiple basic functions like speech development including socialization and communications.

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Rett's Disorder- A genetic disorder commonly seen in girls with unusual locomotoractivity, associated with tapering of the normal development of brain.

Childhood Disintegrative Disorder- It is known as Heller's syndrome, an uncommon condition characterized by late onset of development in language, social communication and motor skills.

Concordance: First degree relatives of ASD are more susceptible. It was estimated that, the pairwise incidences of autism in dizygotic twins is about 31 %, and 88% in monozygotic twins. The survey was including 277 twin pairs, among them 210 were DZT (dizygotic twins) and 67 were MZT (monozygotic twins) under 18 years of age. Here female and male concordance rate was 100% and 86% respectively[10].

Co-morbidity: Co-morbidity is seen frequentlyin ASD.These individuals show associated epilepsy,gastrointestinal disturbance, gastroeso-phageal disturbance,sleep disturbances, eating disorders etc. are common[11].One hundred fifty individuals with autism were studied in their 21styear of age, and they were screened for epileptic seizures. Study estimates the risk of developing epilepsy in autism individuals in 11-39% of cases[12].Though there is a strong genetic factor involvement in ASD, the non-genetic factors are also having strong influence in a considerable extent. The early childhood exposure to infections may influence the immune modification, which makes the individualmore prone for autism.It is observed that more severe GI tract infections are associated with weak immune response[13]. And many of these children are suffering from GI abnormalities like inflammation, infections, etc. The studies have also indicated higher prevalence of GI problems associated with pain in abdomen, constipation, gastro-esophageal reflux, vomiting, diarrhea etc.

Ethnicity: Autism is affecting people of allraces worldwide. From past few decades its incidence hasnotably increased.Ethnicity and immigration factors can influence the incidence of autism. These autism cases are specially recognized in different immigrants worldwide. Though altered sociallife may have some influence on immigrants, mostof the environmental predisposing factors play role ininitiation of subtle changes which may gradually drive the cell metabolism into alteredmolecular pathways[14].

Any link between vaccines and autism incidence?

Vaccination is an inevitable process of immunizing an individual after birth. Recentlyit is observed that the parents are apprehensive regarding vaccination and incidence of autism. The administration of MMR vaccine and its after effects were thought to be a cause for ASD. Administration of multiple vaccines may weaken the immune system of child by causing more threats for infections. This could be one of the notable observations correlated with the ASD incidence worldwideKeeping this in mind different hypotheses were tested to correlate autism incidence.The administration of single vaccine, combinedvaccines andneurotoxic drugs were tested. In this regard the epidemiological and biological surveys in different countries like England, US etc., have failed to show any relevance. Ten year study conducted to compare the annual prevalence of Autism during 1993-2002 ascertained that its incidence was stable during this period[15, 16, 17].

Autism v/s fragile X syndrome;Are they differing? : Fragile X is the genetically inherited condition that causes learning and intellectual disabilitycharacterized by change in one of the genes on the X chromosome, seen approximately 1 in 4,000 males and 1 in 8,000 females.Expansion of CGC

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repeat in the FMR1 genecan be used to distinguish between ASD and FXS, even though there is close similarity in their presentations. But there is lot of conflict that still existsto show association between ASD and FXS.Varied clinical presentations in ASD individuals make the classificationunwieldy.Whereas CNV(Copy-Number Variation)genomic profile is mainly concerned with disease resistance or disease susceptibility in every individual.It may differ in every case. So every genetic disease may stand unique, it is most unlikely to obtain similar and common genetic expressions in all the cases of FXS and autism spectrum disorders. There is broad scope to differentiate them under common diagnostic spectrum[18].

Risk factors:Though there is no direct co-relation of any particular causative factor for ASD. The prenatal exposure to threats during pregnancy may lead into risk. Meta-analysis show statistically significant risk co-relation factors like parental age, maternal gestational diabetes mellitus, bleeding during pregnancy, prenatal medication, intake of psychoactive drugs, general medication etc. A recent observational study has reported that the large difference between the parental ages may be a cause for ASD in their off springs[19, 20].

Recent advancements in ASD: Among multitude of etiologies involved in autism, consensus on role of neurochemicals is most widely accepted. It was evident through number of experiments that the serotonin or 5 hydroxytryptamine plays an important role in development of brain. It is involved in cell division, differentiation, arborization etc. by enhancing the activity of neurotrophic factor 5HT1A. It can enhance the receptor density and number of synaptic contacts to strengthen the activity for longer duration. Thus enhanced potentiation may increase the cognitive ability of an individual [21,22].

The quantity of neurotransmitters, nerve arborization, synaptic contacts, secretions of the neurochemicals are important in establishing a functionally viable brain. GABA, inhibitory neurotransmitter also plays an important role in brain function;underlining its role in autistic personalities. In some of experimental groups the fluctuations in the quantity of neurotransmitter was well noticed. The quantity of Glutamic acid decarboxylase (GAD) enzyme is responsible for the synthesis of gamma-aminobutyric acid (GABA). It is found significantly altered in different parts of brain; it shows the role of GABA on behavior psychology of an individual. Both inhibitory and excitatory neurotransmitters are important for execution of action, whereas in autistics GABA is showing its dominance by reducing activity of firing neurons. Clinically vague signs and symptoms in autistics could be due to fluctuation in the quantity of neurotransmitters in the brain. Imbalance between the GAD and GABA plays an important role in clinically vague signs and symptoms in ASD[23].

Fragile X syndrome is most commonly associated with intellectual disability seen in ASD. A Study shows that FXS is caused by the expansion of CGC repeat in 5' untranslated region of FMR1 gene on Xq27.3. Normally the FMR1 contains 5 to 55 CGG repeats. In the presence of repeats over 200 there is an extensive methylation of CPG Island in the gene promotor region resulting in silencing of FMR1 expression. Premutation alleles with 55-200 repeats are unstable and they ae most likely to express into full mutation when they are maternally transmitted. Based on such underlying genetic factors, the clinical expression in autistic individual patient varies. There is a wide range of intellectual, behavior and

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phenotypic manifestation of FXS. These FXS may display significant dystrophic features associated with marked features like long face, prominent ears, arched plate etc. Man with FXS often displays more exaggerated features of intellectual disability than autistic features. Compared with males, the females exhibit less severe form of phenotypic expressions[24].

These defined areas of mutations, genetic syndromes and denovooccurrence of CNV(Copy-Number Variation)accounting for about only 10-20% ASD. Despite heterogeneity of ASD like biological themes, defective synaptic transmission leading to abnormal brain connectivity is hypothesizedto bethe cause of disease.Where perturbations like lack of inhibitory synaptic response is mainly observed. The difference in the disease manifestationin two groups is based on diversified genetic and environmental factors. Despite variable agreement regarding the developmental onset, an agreement exists that there is more or less a common primary nature of insult.In the glutamatergic transmission reduction of GLUR5 gene product ameliorates ASD like features in FX mice. This model also holds good even to study the seizures observed in ASD[25].

Epigenetic studies give more insight into the ongoing changes in the gene and its expressions. The studies correlate a dominant link with chromosome 15q 11-13. Genomic study has shown chromosome location 1p, 2q, 3p, 7q, 15q and 17q indicating a compelling link with variable expressions in ASD. Even the duplication of chromosome region 15q11-13 in parents is linked with 5% incidence of ASD. Such parents are most likely to transmit the same to their offspring's who are susceptible to show variable degree of ASD[26].Cytogenetic diagnostic insight enables us to take effective measures to avoid unexpected risk. The cytogenetic view also helps the parents to take measures to avoid the possible repetition of such conditions in their offspring's in future.

The radio diagnostic methods can give more insight into structural changes in brain. Where the cortical reconstruction and volumetric segmentation study has helped to understand changes in brain. The autism is affecting the wide areas of the cerebral cortex, but it is difficult to locate a specific area of brain showingvolumetric and geometric features when ASD individuals are compared with normal control group[27].The brain pathology in ASD remains elusive. Assessment of changes at different stages of brain development in young is done by MRI. There are some obvious changes noticed in the hippocampal region of autistic brain. These changes were co-related with the postmortem studies of deceased autism patients. This can give precise insight into the structural changes in brain[28].

Prognosis and life expectancy in ASD: Prognosis in case of autistic individuals is rather limited in relation to long term outcome of disease. However early identification and early intervention may bring some positive changes in ASD[29].The expectancy of life is most important concern among the parents of autistic individuals. It is difficult to keep constant vigilanceonautistic individuals all the time by the parents. Death due to unnatural cause like drowning and epilepsy are reported worldwide. The other causes include trauma, infection, anoxia, cardiac arrest etc. Severity of mental retardation is directly proportional to increased incidence of earlydeath among autistics. Greater fatal risk in autism patients was assessed in a study in California; autism follow-up in 11,347 cases b/w 1983-97 has shown reduced life expectancy. It is much more in male autistic individuals below 5 years of age when compared

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with females at an age ratio 6.1 years and 12.3 years respectively. The death rate of autism patients in male v/s femaleage ratio shows discrimination of 3.1:1[30].

Conflict of interest: Authors would like to declare that they are not having any conflict of interest.

Conclusion- Mental disorders in the society certainly impede the socioeconomic developments in the society. Meeting the health care requirements in ASD is a great burden on poor and middle class families. It is essential to educate the parents, caretakers, teachers; health care provides who handle the autistic patients. Education in general population can create conduciveenvironment without isolating and discriminating the autistic population from the main stream. Epidemiological statistics are important to make government policies on health care, education and rehabilitation.

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