IJPSR (2016), Vol. 7, Issue 9 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 28 March, 2016; received in revised form, 02 August, 2016; accepted, 08 August, 2016; published 01 September, 2016

AUTISM: AN EARLY-ONSET NEURODEVELOPMENTAL DISORDER

Ashwani Arya * and Gulshan Sindhwani

Department of Pharmaceutical Education and Research, BPS Women University, South Campus, Bhainswal Kalan, Sonipat, Haryana, India.

Keywords:

Autism, Dopamine, GABA, Genetic, Serotonin

Correspondence to Author:
Ashwani Arya

Assistant Professor
Department of Pharmaceutical Education and Research, BPS Women University, South Campus, Bhainswal Kalan, Sonipat Haryana, India.

Email: ashwaniarya5@rediffmail.com

ABSTRACT: Autism is an early-onset neurodevelopmental disorder characterized by difficulties in social interaction and communication, and the repetitive interests or restricted interests and behaviors. Approximately 67 million people are affected by autism around the world. Autism has increased to epidemic proportions, affecting four times as many males and females. The exact etiology of autism remains largely unidentified; however, literature has emerged to propose the genetic, neurological, environmental and immunological contributions play critical roles in the enlargement of autism. Autism is well known as a complex developmental disorder with a seemingly confusing and uncertain pathogenesis. The serotonin, dopamine, glutamate, GABA, cytokinin thought to contribute to the pathophysiology of autism. These areas of research have contributed to the development of a number of medications currently in use for interfering symptoms, and may guide the future development of novel agents. This review will cover the understanding on the clinical sign and symptoms, its causes, diagnosis, pathophysiology and neuronal circuits involved in autism.

INTRODUCTION: Autism is a global health crisis that knows no borders - it does not discriminate based on nationality, ethnicity or social status. Autism is a childhood-onset neurodevelopmental disorder characterized by impairment in reciprocal social interactions, communication and repetitive and stereotyped behavioural patterns [1]. Approximately 67 million people are affected by autism around the world [2]. Autism has increased to epidemic proportions, affecting four times as many males and females. Autism is a complex disorder that is heterogeneous in nature, with varying degrees of severity and for which no specific biological marker has been identified.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.7(9).3567-75

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7 (9).3567-75

The increasing prevalence of autism is raising public-health concerns. The estimated lifetime per capita incremental societal cost of autism is $3.2 million. Lost productivity and adult care are the largest components of the cost [3, 4]. Greater than the monetary cost, the emotional devastation caused by the great difficulties posed by the autistic individual, and the strains on the family, cause long-lasting strife and sometimes physical threats to the autistic individual and to others around them. A great deal of research and funding has been devoted to understanding the cause of autism [5].

Autism comorbidy with seizures and mental retardation occurs in up to 30% and in 80% of autistic patients, respectively. The exact etiology of autism remains mostly unknown; however, literature has emerged to suggest the neurological, environmental, genetic, and immunological play critical roles in the development of autism [6, 7]. The monoamines, glutamate and gamma-aminobutyric acid (GABA), neuropeptides, inflammatory and

immune processes thought to contribute to the pathophysiology of autism [8-11]. These areas of study have contributed to the development of a number of medications in use for interfering the symptoms and may guide the upcoming development of novel agents [12].

Clinical Sign and Symptoms of Autism: Clinically, autism is defined by a "triad" of deficits comprising difficulties in social interaction and communication, and repetitive or restricted interests and behaviors. Autism is distinguished by a pattern of symptoms rather than one single symptom [1, 13]. The clinical features of the autism are summarized in the **Fig. 1**.

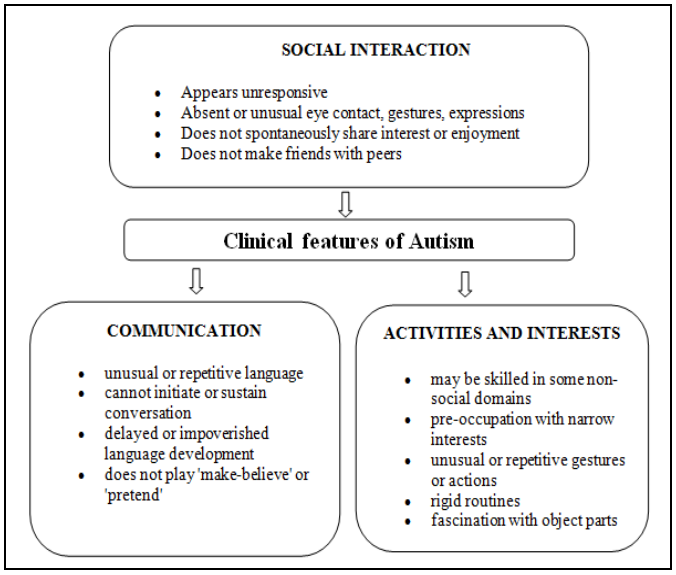

FIG.1: CLINICAL FEATURES OF AUTISM

Causes of Autism: Autism is thought to be an inherited disorder. However, the mutations that increase the risk of autism have not been recognized. Typically, autistic disorder cannot be traced to a Mendelian (single-gene) mutation or to single chromosome abnormalities such as fragile X syndrome or 22q13 deletion syndrome [14]. There may be significant interactions among mutations in several genes, or between the mutated genes and environment [15, 16]. All known teratogens related to the risk of autism appear to act during the first eight weeks from conception [16]. Environmental factors that contribute to or exacerbate autism, and important in upcoming research, include heavy metals, certain foods, solvents, infectious disease, phthalates, phenols and diesel exhaust used in pesticides alcohol, brominated flame retardants illicit drugs plastic products, vaccines smoking [17]. The risk of autism is associated with several prenatal and perinatal risk factors. Such risk factors included advanced maternal age, highly developed paternal age, A number of medical setting linked with syndromic autism come out to influence and potentially interrupt the neurodevelopmental processes, including cortical connectivity, brain growth, and neurotransmitters pathways. These neurobiological alterations probable influence the developmental route of social behavior and communication during premature stages of infancy and determine the unusual clinical phenotypes of autism [18].

Pregenency: The placenta is a major endocrine organ with endocrine, paracrine, and autocrine effects [19]. The placenta makes progesterone that maintains the pregnancy, relaxing the gravid uterus and inhibiting fetal rejection by suppression of maternal lymphocyte activity. In addition, placental progestins enter the maternal and fetal circulation, crossing the blood-brain barrier to promote both maternal and fetal neurogenesis. The placenta produces inflammatory (i.e., IL-6) and anti-inflammatory (i.e., IL-10) cytokines that would influence both the fetus and the mother. Oxytocin concentrations have been linked to social behavior, and oxytocin pathway signaling may be impaired in autism. It is suggested that autism can be "programmed" by placental signals that fundamentally and permanently change the way the fetus is wired [19, 20]. Maternal immune activation due to prenatal viral exposure can lead to an increase in maternal IL-6 levels and altered gene expression, which potentially could precipitate autistic behavior and neuropathology in the fetus later in time or after birth [20, 21]. Production of IL-2, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α may result in demyelination and oligodendrocyte damage, thereby playing a function in the pathogenesis of autism [22, 23].

Neurotoxicity of mercury: Mercury is known to be neurotoxic and has effects on the immune system. Mast cells are concerned in allergic reactions, innate and acquired immunity and inflammation. Mercury stimulates interleukin (IL)-6 and vascular endothelial growth factor and release from mast cells. These mediators could interrupt the blood–brain barrier and cause brain inflammation [24].

Screening: Most parents notice their children's unusual behaviors by age 18 to 24 months. Some of the early signs for the child to be evaluated by a specialist without delay include: No babbling by 12 months, no gesturing (pointing, waving goodbye) by 12 months. No single words spoken by 16 months, no two-word spontaneous phrases (not including echolalia) by 24 months, loss of any form of language or social skills, at any age. Screening tools include the Modified Checklist for Autism in Toddlers (M-CHAT) [25]. The Early Screening of Autistic Traits Questionnaire, and the First Year Inventory. Screening tools designed for one culture's norms for behaviors like eye contact may be inappropriate for a different culture [26].

Diagnosis of Autism: Autism is defined in the diagnostic and statistical manual IV ((DSM-IV-TR) as exhibiting at least a total of six symptoms, counting at slightest two symptoms of the qualitative impairment in social interaction, at least one warning sign of qualitative impairment in communication, and at least one notice sign of repetitive and restricted behavior. The Childhood Autism Rating Scale (CARS) is used extensively in clinical environments to evaluate severity of autism based on observation of children in autism [27-29]. A pediatricians usually perform a preliminary analysis by taking the developmental record and physically examining the child. If warranted, evaluations and diagnosis are conducted with assist from autism specialists, observing and assessing communication, cognitive and family. Differential identification for autism at this phase might also consider mental retardation, hearing impairment, and specific language impairment [27].

In excess diagnosis and under diagnosis are troubles in cases of marginal and a lot of the existing increase in the number of reported autistic cases may be due to changes in diagnostic practices. It is mainly hard to analyze autism among the visually impaired, to some extent because a little of its diagnostic criteria depend on the vision and partly because autistic symptoms overlap with those of general blindness syndromes [28, 29].

The diagnostic criteria for autism comprise three wide areas of impairment. The first relates to social interaction, with deficits in expression and gesture, social and emotional reciprocity, and allocation of curiosity. A second region of impairment is in communication, with the behaviors deficits ranging from spoken language to symbolic play. The third includes activities and interests, restricted and activities of stereotyped and encompass rigid preferences for routine as well as repetitive motor mannerism [30]. The features of autism are often referred to as a "triad of impairments", impairments of social might be opening, as longitudinal studies propose that early social deficits present near perfect classification of later diagnosis. Early initiation of psychosocial treatments and careful psychopharmacological management of co-occurring diagnoses are required for the best behavioral outcomes [31, 32].

Pathophysiology of Autism: Research in to the pathophysiology and etiology of autistic disorder (autism) has been ongoing for nearly a half century. The neurotransmitters are potent chemicals that regulate numerous physical and emotional processes such as emotional states, pain response and mental performance [33]. Various functions in life are regulated by neurotransmitters. They are the brain's chemical messengers. Interactions between the brain chemicals, hormones and neurotransmitters have a profound impact on the overall health and well-being. Serotonin (5-HT), glutamate, GABA, and dopamine (DA) are neurotransmitters that are critical for neurodevelopment, including migration, differentiation, cell proliferation, synaptic plasticity, apoptosis, and synaptogenesis [34-36]. The strongest evidence implicates the glutamatergic, GABAergic and serotonergic systems, with weaker evidence for cholinergic systems, catechol-aminergic and peptidergic [37, 38]. Most neurochemical ressearch on autism has focused on monoamines, although peptides, (amino acids, and metabolites, including y-aminobutyric acid (GABA) and excitatory amino acids, acetylcholine and other neuromodulators, may be implicated in the pathophysiology of autism [11, 18, 34].

Serotonin: Serotonin is the earliest developing neurotransmitter system in the brain, and ultimately becomes the mostly usually distributed system in the brain, contacting most cells of the cortex [38-41]. Dysfunction in the systems of dopaminergic and

noradrenergic in the neocortex-subcortical structure-cerebellum pathway is the core of the pathogenesis of autism [36, 42]. Serotonin is the neurotransmitter involved in modulating adult cortical plasticity and known to have a critical role in early cortex development by regulating proliferation, migration and neuronal differentiation [38, 43]. Serotonin acts via seven families of receptors (5-HT1 – 5-HT7) and is related to memory, mood, endocrine functions, sleep, learning, and muscle contraction homeostasis [44-46].

Abnormalities in the serotonergic system are thought to cause disturbances in the sleep/arousal rhythm observed from the early stages of autism spectrum disorders, poor social skills, and adaptation disorder to a new environment [36, 42]. During brain development, serotonin has been shown to influence the maturation of target tissues, including neurogenesis, synaptogenesis, dendritic elaboration and organization of the cortex [41, 47]. At early stages of growth, when the blood–brain barrier is not yet completely formed, the serotonin be able to enter the brain of a developing fetus, and cause a loss of serotonin terminals through negative response. This loss of serotonin innervations persists throughout subsequent development and the symptoms of autism appear [35, 44]. Thus, accumulating facts indicates that serotonergic projections undergo continuous age-related change through early childhood. A number of studies have examined the relationship between autism and abnormalities in the serotonin neuron system, and these abnormalities are considered to be the core of the pathogenesis of autism spectrum disorders [44].

Glutamic acid: Glutamic acid is essential for the development and plasticity of the cerebral cortex, and is dependable for the collaborative function with serotonin in the development of the thalamocortical pathway. Glutamate has many roles throughout the brain and nervous system. Glutamate is an excitatory transmitter: when it is released it increases the chance that the neuron will fire. This enhances the electrical flow among brain cells required for normal function and plays an important role during early brain development. It may also assist in learning and memory [10]. Glutamate is elevated in plasma and CSF in many children with autism. Increased expression of the glutamate transporter and polymorphisms in genes encoding metabotropic and ionotropic glutamate receptors are also reported in autism. These amino acid alterations may be caused by immune mediated events, vitamin insufficiency, alterations in neurotransmitter transport, or metabolic derangement. Changes in amino acid levels may lead to elevated or insufficient neurotransmitter activity and thus can interfere with normal cognitive development [10, 48].

GABA: GABA has a key role in the regulation of early developmental stages of cell migration, neuronal differentiation and stages of maturation [49]. Besides, formation of GABAergic system has a critical role in migration of GABAergic neurons and formation of glutamergic system mediated excitatory processes that regulate cortical inhibitory system [50]. GABA is the primary inhibitory neurotransmitter in the brain. It inhibits nerve transmission in the brain, calming nervous activity. Reduced GABA transmission has been linked with impaired sleep, hyperkinesis, seizures, mental retardation, hyperactivity and impaired motor coordination [51]. Several findings propose a function for the GABAergic system in autism. There are information of decrease of the GABAergic system enzymes, elevated plasma GABA levels, and decreased availability of GABA in autistic patients. Lower GABA levels could reduce the threshold for rising seizures which are often linked with autism [11, 51].

Dopamine: Dopamine acts through five receptors (D1 – D5) and modulates multiple brain functions, including reward response, attention, memory, problem solving, and motivation which is critical to control voluntary movements [45]. In general, the dopaminergic system is thought to affect a wide range of behaviors and functions, including cognition, brain-stimulation reward mechanisms, motor function, drinking behaviors, eating, sexual behavior, selective attention and neuroendocrine regulation [36, 52]. The cell bodies of the dopamine neuron system are distributed in a concentrated manner at the midbrain substantia nigra pars compacta and ventral tegmental area. Dopamine neurons are also localized in the pathway of mesocorticolimbic dopaminergic, which has projections to the ventral tegmental area, amygdala, olfactory tubercule, accumbens nucleus, septal

area, and prefrontal area, and is deeply concerned in functions such as reward behavior, motivation, cognitive function, and sustained attention [36]. A dopamine transporter, localized at the membrane of the cell, plays an essential function in dopamine metabolism by incorporating extracellular dopamine into the cell and decreasing the concentrations of extracellular dopamine. Once released from the neuron, central Dopamine is broken down into HVA (homovanillic acid) and 3,4- (DOPAC (dihydroxyphenylacetic acid).

Genetic studies of dopamine involvement in autism have suggested possible involvement of the A1 allele of the dopamine D_2 receptor gene. The cell bodies of the dopamine neuron system are distributed in a concentrated manner at the midbrain substantia nigra pars compacta and ventral tegmental area. Dysfunction in the dopaminergic and noradrenergic system in the neocortex (prefrontal area)-subcortical structure (the caudate nucleus, putamen, pallidum, and thalamus) - cerebellum pathway is the core of the pathogenesis of autism [52, 53].

Cytokines: Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system. Cytokines are a category of signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis. Cytokines are produced throughout the body by cells of diverse embryological origin. Cytokine is a general name; other names are defined based on their presumed function, cell of secretion, or target of action [5, 20, 54].

Interestingly, an emerging body of evidence is growing concerning the link between abnormal immune function and neurological dysfunction with autism spectrum disorders. During the critical times of the infantile development, immune dysregulation may outcome in the release of immunomodulatory molecules, such as cytokines and chemokines, leading to changed neural function and neuronal development [9, 46, 55]. Many studies reveal increased levels of pro-inflammatory cytokines in brain, cerebrospinal fluid (CSF), and blood from children with autism. Inflammatory cytokines including tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-1β and IL-12 are elevated in the blood mononuclear cells, plasma and serum of autistic subjects. Studies have shown that peripheral activation of cytokines can lead to central nervous system release of various neurotransmitters. Specifically, IL-1 administration may promote CNS release of serotonin, dopamine, norepineprhine, glutamate, and gammaamino-butyric-acid [56, 57]. With the enhanced turnover of these neurotransmitters, significant behavioral and neurological alterations transpire. In Furthermore, Ashwood and colleagues (2008) found that reduced levels of the modulatory cytokine, transforming growth factor-β1 in autistic children contributed to the dysregulation of adaptive behaviors and predisposal for autoimmune responses [5, 58].

Vojdani and coauthors (2008) study decreased the natural killer cell activity in autistic children with low intracellular levels of glutathione, IL-2, and IL-15 [59]. Decreased natural killer cell activity has been associated with autoimmunity through alteration of cytokine production. [32] Autoimmunity can be detrimental to normal neuronal signaling and result in significant behavioral abnormalities [70]. Recent studies have also demonstrated that transforming macrophage chemoattractant protein -1, growth factor-β1, IL-6, IL-10, IFN-γ, IL-8 and TNF-α are increased in the frontal cortices of autistic brains. Furthermore, IL-6, MCP-1, IL-8, IFN-γ and TNF-α were found to be significantly increased in the CSF of autistic children [5, 54, 55]. Therefore, the abnormalities of one of these neurotransmitters could be detrimental for neuronal development and potentially be associated with abnormal neuronal function in autism. Periodic diagnosis of this neurotransmitter will provide a basement for the efficient and effective therapy [54, 55].

Imbalance in Neural Systems of Autism: Neuroimaging research has revealed a broad network of regional brain abnormalities in autism, including cerebellum, frontal, parietal, limbic regions, and basal ganglia [60]. The cerebellar dysfunction may be important in the etiology of the disorder [61, 62]. Particularly cerebellum implicated in deficits of long-range connectivity and coordination of cognitive functions, which is the common sites of anatomic abnormality in autism [63]. Neurobehavioral studies have shown associations between cerebellar anatomic abnormality and certain motor, cognitive, and social deficits. [64]

Three major types of defects have been revealed in autism: the limbic system (hippocampus and amygdala), the cerebellum and brainstem and the cortex [65]. Abnormal regulation of brain growth in autism results in early overgrowth followed by abnormally slowed growth [63]. It has been said that people with autism suffer from a lack of "central coherence" and the cognitive capability to bind together a jumble of separate features into a single, coherent object or concept. Many major brain structures include cerebellum, cerebral cortex, limbic system, corpus callosum, basal ganglia, and brain stem are implicated in autism [66]. The major brain structures implicated in autism are summarized in the **Table 1**.

The cytoarchitectonic abnormalities present in autistic brains are most compatible with reduced programmed cell death and/or increased unusual cell proliferation, cell migration and altered cell differentiation with condensed neuronal size, each one pointing toward the first/second trimester of pregnancy as the critical time for deranged neurodevelopment in autism. [65-68]. The abnormalities in regions of brain stem-subcortical structure, cerebellum network, hippocampus, cingulate gyrus, and piriform acting a central part in the pathogenesis of autism [60]. A mainly strong rationale has been developed for connection of the amygdala and related areas of the limbic cortex [68-70]. More specifically, the core social relatedness deficits in autism disorders serve to focus interest on the rostral limbic system, including the medial orbitofrontal cortex, amygdala, septum, anterior insular cortex, anterior cinglate cortex and the nucleus accumbens [60, 63, 70].

TABLE 1: THE MAJOR BRAIN STRUCTURES IMPLICATED IN AUTISM [66]

S. No	Brain Parts	Brain Structure implicated in Autism
1.	Cerebral Cortex	A thin layer of gray matter on the surface of the cerebral hemisphere. Two thirds of its area is deep in the fissures or folds. Responsible for the mental function, general movement, perception and behavioral reaction.
2.	Amygdala	Responsible for emotional response including aggressive behavior.
3.	Hippocampus	Make it possible to remember new information and recent events.
4.	Basal Ganglia	Gray masses deep in the cerebral hemisphere that serves as connection between cerebrum and cerebellum. Helps to regulate automatic movement.
5.	Corpus Callosum	Consists primarly of closely placed bundles of fibres that connect the right and left hemisphere and allows for communication between the hemisphere.
6.	Brain stem	It serve as a relay station, passing message between various parts of the body and the cerebral cortex. Primitive function essential to survival (breathing and heart rate control) are lacated here.
7.	Cerebellum	It fine tunes our motor activity, regulate balance, body movements, coordination and the muscles used for speaking .

CONCLUSION: Autism is a classified as complex neurodevelopmental disabilities, which is characterized by significant difficulties in social, communicative, and behavioral functioning. Given the consequence of autism for understanding of normative and unusual development of social behavior, investigation in autism has the potential to crucially update awareness in biological, medical, social and behavioral sciences. Consequently, research continues to improved understand the composite development of autism, to discover disease-specific interventions, and improved conduct to enable communities to give resources for families.

ACKNOWLEDGMENT: The author was conveys deep sence of gratitude to the DPER, Bhagat Phool Singh Women University for their continuous support and inspiration.

REFERENCES:

1. Matson JL, Kozlowski AM and Matson MM: Speech deficits in persons with autism: Eitiology and symptom presentation. Res Autism Spectr Disor 2012; 6: 573-577.
2. Patricia B, Kopetz and Desmond E: Autism Worldwide: Prevalence, Perceptions, Acceptance, Action. Journal of Social Sciences 2012; 8 (2): 196-201.
3. Blumberg SJ, Bramlett MD, Kogan MD, Schieve LA, Jones JR and Lu MC: Changes in prevalence of parent-reported autism spectrum disorder in school-aged U.S. children: 2007-2012. Natl Health Stat Report 2013; 65: 1-11.
4. Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, Miller J, Fedele A, Collins J, Smith K, Lotspeich L, Croen LA, Ozonoff S, Lajonchere C,

Grether JK and Risch N: Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry 2011; 68: 1095–1102.
5. Depino AM: Peripheral and central inflammation in autism spectrum disorders. Mol Cell Neurosci 2013; 53: 69–76.
6. Murdoch JD and State MW: Recent developments in the genetics of autism spectrum disorders. Curr Opin Genet Dev 2013; 23: 310–5.
7. Chaste P and Leboyer M: Autism risk factors: genes, environment, and gene-environment interactions. Dialogues in Clinical Neuroscience 2012; 14: 281–292.
8. Sgadò P, Genovesi S, Kalinovsky A, Zunino G, Macchi F, Allegra M, Murenu E, Provenzano G, Tripathi PP, Casarosa S, Joyner AL and Bozzi Y: Loss of GABAergic neurons in the hippocampus and cerebral cortex of Engrailed-2 null mutant mice: implications for autism spectrum disorders. Exp Neurol 2013; 247: 496–505.
9. Alabdali A, Ayadhi L and Ansary A: Association of social and cognitive impairment and biomarkers in autism spectrum disorders. Journal of Neuroinflammation 2014; 11 (4): 2-14.
10. Elst LTV, Maier S, Fangmeier T, Endres D, Mueller GT, Nickel K, Ebert D, Lange T, Hennig J, Biscaldi M, Riedel M and Perlov E: Disturbed cingulate glutamate metabolism in adults with high-functioning autism spectrum disorder: evidence in support of the excitatory/inhibitory imbalance hypothesis. Molecular Psychiatry 2014; 19: 1314–1325.
11. Wei H, Zou H, Sheikh AM, Malik M , Dobkin C , Brown WT and Li X: IL-6 is increased in the cerebellum of autistic brain and alters neural cell adhesion, migration and synaptic formation. Journal of Neuroinflammation 2011; 8 (52): 1-10.
12. Penagarikano O: New Therapeutic Options for Autism Spectrum Disorder: Experimental Evidences. Exp Neurobiol 2015; 24 (4): 301-11.
13. APA. Diagnostic and Statistical Manual of Mental Disorders 5th Ed. Washington, DC: American Psychiatric Association 2013.
14. Abrahams B S and Geschwind D H: Advances in autism genetics: on the threshold of a new neurobiology. Nat Rev Genet 2008; 9 (5): 341–55.
15. Schaefer GB and Mendelsohn NJ: Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med 2013; 15: 399–407.
16. Zerbo O, Qian Y, Yoshida C, Grether JK, Water JVD and Lisa A. Croen Maternal Infection During Pregnancy and Autism Spectrum Disorders. Journal of Autism and Developmental Disorders 2015; 45(12): 4015-25.
17. Kolevzon A, Gross R and Reichenberg A: Prenatal and perinatal risk factors for autism. Arch Pediatr Adolesc Med 2007; 161(4): 326–33.
18. Benvenuto A, Manzi B, Alessandrelli R and Galasso C: Recent Advances in the Pathogenesis of Syndromic Autisms: Curatolo. International Journal of Pediatrics 2009; 1-9.
19. Patterson P H: Maternal infection and immune involvement in autism. Trends in Molecular Medicine 2011; 17 (7): 389–94.
20. Lenroot RK and Yeung PK: Heterogeneity within Autism Spectrum Disorders: What have We Learned from Neuroimaging Studies? Front Hum Neurosci 2013; 7: 733-38.
21. Parker-Athill EC and Tan J: Maternal Immune Activation and Autism Spectrum Disorder: Interleukin-6 Signaling as a Key Mechanistic Pathway. Neurosignals 2010; 21-30.
22. Atladottir HO, Thorsen P, Ostergaard L, Schendel DE, Lemcke S, Abdallah M and Parner ET: Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. J. Autism Dev. Disord 2010; 40: 1423–30.
23. Lyall K, Schmidt RJ and Hertz PI: Maternal lifestyle and environmental risk factors for autism spectrum disorders. Int J Epidemiol 2014; 43 (2): 443–64.
24. Kempuraj D, Asadi S, Zhang B, Manola A, Hogan J, Peterson E and Theoharides T C: Mercury induces inflammatory mediator release from human mast cells. J. Neuroinflammation 2010; 7: 20-.27.
25. Wetherby AM, Brosnan-Maddox S, Peace V and Newton L: Validation of the Infant-Toddler Checklist as a broadband screener for autism spectrum disorders from 9 to 24 months of age. Autism 2008; 12: 487–511.
26. Tsai LY: Impact of DSM-5 on epidemiology of Autism Spectrum Disorder. Res Autism SpectrDisord. 2014; 8(11): 1454–70.
27. Taurines R, Schwenck C, Westerwald E, Sachse M, Siniatchkin M and Freitag C. ADHD and autism: differential diagnosis or overlapping traits? A selective review. Atten Defic Hyperact Disord 2012; 4: 115–39.
28. Won H, Mah W and Kim E: Autism spectrum disorder causes, mechanisms, and treatments: focus on neuronal synapses. Front Mol Neurosci. 2013; 6(5): 19-25.
29. Lai MC, Lombardo MV and Baron-Cohen S: Autism. Lancet 2014; 383 (9920): 896–910.
30. Stoner R, Chow ML, Boyle MP, Sunkin SM, Mouton PR, Roy S, Wynshaw-Boris A, Colamarino SA, Lein ES and Courchesne E: Patches of disorganization in the neocortex of children with autism. N Engl J Med 2014; 370: 1209–19.
31. Chen JA, Penagarikano O, Belgard TG, Swarup V and Geschwind DH: The emerging picture of autism spectrum disorder: genetics and pathology. Annu Rev Pathol 2015; 10: 111–44.
32. Thapar A, Cooper M, Eyre O and Langley K: What have we learnt about the causes of ADHD? J Child Psychol Psychiatry 2013; 54(1): 3-16.
33. Carla AM, Herrington J, Siegel M, Scarpa A, Brenna BM, Scahill L and Susan WW: The Role of Emotion Regulation in Autism Spectrum Disorder. J of American academy of child and adolescent Psychiatry 2013; 52(7): 679–88.
34. Ecker C, Bookheimer SY, Murphy DG: Neuroimaging in autism spectrum disorder: brain structure and function across the lifespan. Lancet Neurol 2015; 14: 1121-34.
35. Adamsen D, Ramaekers V, Ho HTB, Britschgi C, Rüfenacht V, Meili D, Bobrowski E, Philippe P, Nava C, Maldergem LV, Bruggmann R, Walitza S, Wang J, Grünblatt E, and Thöny B: Autism spectrum disorder associated with low serotonin in CSF and mutations in the SLC29A4 plasma membrane

monoamine transporter (PMAT) gene. Molecular Autism 2014; 43 (5): 2-11.
36. Hamilton PJ, Campbell NG and Sharma S: De novo mutation in the dopamine transporter gene associates dopamine dysfunction with autism spectrum disorder. Mol. Psychiatry 2013; 18: 1315–23.
37. Berg AT and Dobyns WB: Progress in autism and related disorders of brain development. Lancet Neurol 2015; 14: 1069-70.
38. De GE, Serrano M, Perez BD, Ormazabal A, Montero R, Veneselli E, Pineda M, Gonzalez V, Sanmarti F, Fons C, Sans A, Cormand B, Puelles L, Alonso A, Campistol J, Artuch R and Garcia AC: Cerebrospinal fluid alterations of the serotonin product, 5-hydroxyindolacetic acid, in neurological disorders. J Inherit Metab Dis 2010; 33: 803–9.
39. Azmitia EC, Singh JS and Azmitia PMW: Increased serotonin axons (immunoreactive to 5-HT transporter) in postmortem brains from young autismdonors. Neuropharmacol 2011; 60: 1347–54.
40. Hadjikhani N: Serotonin, pregnancy and increased autism prevalence: is there a link? Med Hypothesis 2010; 74:880–883.
41. Yang CJ, Tan HP and Du YJ: The developmental disruptions of serotonin signaling may be involved in autism during early brain development. Neuroscience 2014; 267:1–10.
42. Wegiel J, Kuchna I, Nowicki K, Imaki H, Marchi E, Ma SY, Chauhan A, Chauhan V, Bobrowicz TW, de Leon M, Louis LA, Cohen IL, London E, Brown WT, Wisniewski T: The neuropathology of autism: defects of neurogenesis and neuronal migration, and dysplastic changes. Acta Neuropathol 2010; 119: 755–70.
43. Seo D, Patrick CJ and Kennealy PJ: Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders. Aggress Violent Behav 2008; 13: 383–95.
44. Celada P, Puig MV and Artigas F: Serotonin modulation of cortical neurons and networks. Front Integr Neurosci 2013; 7: 25.
45. Meyer RR: A review of the serotonin transporter and prenatal cortisol in the development of autism spectrum disorders. Molecular Autism 2013; 37 (4): 2-16.
46. Wei AEH, Kathryn K, Chadman C, Daniel P, McCloskey D, Ashfaq M, Sheikh A, Malik AWM, Brown BT and Li AX: Brain IL-6 elevation causes neuronal circuitry imbalances and mediates autism-like behaviors. Biochimica et BiophysicaActa 2012; 831–42.
47. Ha S, Sohn IJ, Kim N, Sim HJ and Cheon KA: Characteristics of Brains in Autism Spectrum Disorder: Structure, Function and Connectivity across the Life span. Exp Neurobiol 2015; 24 (4): 273-84.
48. Horder J, Lavender T, Mendez MA, Gorman RO, Daly E and Craig MC: Reduced subcortical glutamate/glutamine in adults with autism spectrum disorders: MRS study. Transl. Psychiatry 2013; 279 (3): 2013-53.
49. Coghlan S, Horder J, Inkster B, Mendez MA, Murphy DG and Nutt DJ: GABA system dysfunction in autism and related disorders: from synapse to symptoms. Neurosci. Biobehav Rev 2012; 36: 2044–55.
50. Hubner CA and Holthoff K: Anion transport and GABA signaling. Front Cell Neurosci 2013; 7: 177.
51. Deidda G, Bozarth IF and Cancedda L: Modulation of GABAergic transmission in development and neurodevelopmental disorders: investigating physiology and pathology to gain therapeutic perspectives. Front Cell Neurosci 2014; 8: 1-23.
52. Money KM, Stanwood GD: Developmental origins of brain disorders: roles for dopamine. Front Cell Neurosci 2013; 7: 260.
53. Spencer T, Biederman J, Madras BK, Dougherty DD, Bonab AA, Livni E, Meltzer PC, Martin J, Rauch S and Fischman AJ: Further evidence of dopamine transporter dysregulation in ADHD: A controlled PET imaging study using altropane. Biological Psychiatry 2007; 62: 1059-61.
54. Hsiao EY: Immune dysregulation in autism spectrum disorder. International Review of Neurobiology 2013; 113: 269–302.
55. Ashwood P, Krakowiak P, Hertz PI, Hansen R, Pessah I and Van WJ: Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. Brain BehavImmun 2011; 25: 40–45.
56. Maximo JO, Cadena EJ and Kana RK: The implications of brain connectivity in the neuropsychology of autism. Neuropsychol Rev 2014; 24: 16-31.
57. Coghlan S, Horder J, Inkster B, Mendez MA, Murphy DG, Nutt DJ: GABA system dysfunction in autism and related disorders: From synapse to symptoms. NeurosciBiobehav Rev 2012, 36: 2044–55.
58. Ashwood P, Enstrom A, Krakowiak P, Hertz-Picciotto I, Hansen RL and Croen LA: Decreased transforming growth factor beta1 in autism: A potential link between immune dysregulation and impairment in clinical behavioral outcomes. Journal of Neuroimmunology 2008; 204(1-2): 149-53.
59. Vojdani A, Mumper E, Granpeesheh D, Mielke L, Traver D and Bock K: Low natural killer cell cytotoxic activity in autism: The role of glutathione, IL-2 and IL-15. Journal of Neuroimmunology 2008; 205:148-54.
60. Lange N, Travers BG, Bigler ED, Prigge MB, Froehlich AL, Nielsen JA, Cariello AN, Zielinski BA, Anderson JS, Fletcher PT, Alexander AA and Lainhart JE: Longitudinal volumetric brain changes in autism spectrum disorder ages 6-35 years. Autism Res 2015; 8: 82-93.
61. Fatemi SH, Aldinger KA, Ashwood P, Bauman ML, Blaha CD and Blatt GJ: Consensus paper: pathological role of the cerebellum in autism. Cerebellum 2012; 11(3): 777–807.
62. Stoodley CJ: Distinct regions of the cerebellum show gray matter decreases in autism, ADHD, and developmental dyslexia. Front. Syst. Neurosci 2014; 8: 92-99.
63. Giarelli E, Wiggins LD, Rice CE, Levy SE, Kirby RS, Pinto-Martin J and Mandell D: Sex differences in the evaluation and diagnosis of autism spectrum disorders among children. Disabil Health J. 2010; 3: 107-16.
64. Choi US, Kim SY, Sim HJ, Lee SY, Park SY, Jeong JS, Seol KI, Yoon HW, Jhung K, Park JI and Cheon KA: Abnormal brain activity in social reward learning in

children with autism spectrum disorder: an fMRI study. Yonsei Med J 2015; 56: 705-11.
65. Lynch CJ, Uddin LQ, Supekar K, Khouzam A, Phillips J and Menon V: Default mode network in childhood autism: posteromedial cortex heterogeneity and relationship with social deficits. Biol Psychiatry 2013; 74: 212-19.
66. National Institute of Mental Health (NIMH) 2007.
67. Moseley RL, Ypma, RJF, Holt RJ, Floris D, Chura LR, Spencer MD, Baron-Cohen S, Suckling J, Bullmore E and Rubinov M: Whole-brain functional hypoconnectivity as an endophenotype of autism in adolescents. NeuroImage Clin 2015; 9: 140–52.
68. Dziobek I, Bahnemann M, Convit A and Heekeren HR: The role of the fusiform-amygdala system in the pathophysiology of autism. Arch. Gen. Psychiatry 2010; 67:397–405.
69. Philip RCM, Dauvermann, MR, Whalley HC, Baynham K, Lawrie SM and Stanfield AC: A systematic review and meta-analysis of the fMRI investigation of autism spectrum disorders. Neurosci. Biobehav. Rev. 2012; 36: 901–42.
70. Pessoa L: Beyond brain regions: network perspective of cognition-emotion interactions. Behav. Brain Sci. 2012; 35: 158–59.

How to cite this article:
Arya A and Sindhwani G: Autism: An early-onset Neurodevelopmental disorder. Int J Pharm Sci Res 2016; 7(9): 3567-75.doi: 10.13040/IJPSR.0975-8232.7(9).3567-75.