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Review Article

Global prevalence and etio-pathogenesis of autism: a review

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ABSTRACT

Autism spectrum disorder (ASD) is a complicated neurobehavioral disorder, characterized by lack of social communication, presence of restricted and repetitive behaviors and lack of verbal development. The condition is believed to stem from cerebral malfunctioning resulting from a complex interplay of environmental, genetic and epigenetic variables. The level and number of symptoms vary from individual to individual and hence the clinical findings cannot be generalized. Prevalence of ASD has risen over the years which is possibly due to increased diagnosis, reporting and awareness. Autistic individuals are observed to have certain physiological challenges as abnormalities in the gut-brain axis with a focus on gut dysbiosis. This current review was prepared using PubMed, Google Scholar and other sources. It presents data on the primary streams about the etio-pathogenesis and global prevalence of ASD. However, it is observed that there is no specific cure for ASD. Timely intervention results in significant enhancements in social communication abilities, cognitive and adaptive functions.

Keywords: Autism, Epigenetic, Gut dysbiosis, Prevalence, Etio-pathogenesis

INTRODUCTION

Autism spectrum disorder (ASD) encompasses a range of neuro-developmental characteristics having varied degrees of repetitive behaviors, restricted interests, impaired social communication and interaction.[1] These conditions arise from atypical brain development. ASD can have far-reaching effects on physiological systems, including the immune, endocrine and gut microbiome systems.[2] ASD imposes a substantial social and economic burden globally, with a prevalence ranging from 0.5% to 2%.[3] While genetics play a significant role in ASD, the rapid increase in prevalence cannot be attributed solely to genetic factors.[1] Recent epidemiological studies suggest that maternal and neonatal factors may also contribute to the development of ASD.[3]

EPIDEMIOLOGY

ASD is widely considered as having a strong genetic basis, with heritability estimates ranging from 70% to 90%.[4] Males may be more susceptible to ASD due to the presence of X-chromosome linked genes, while females are less probable for autism diagnosis due to various factors making their presentations less visible and recognized by society.[5] The prevalence of autistic disorder was 1.00 per 1,000 individuals, varying from 0.19 in Germany to 7.26 in Sweden.[6] Between 1990 and 2006, a total of 31,307 children under 10 years of age received their initial autism diagnosis. Notably, the vast majority (98.5%) of these diagnoses were based on comprehensive developmental evaluations, while a smaller percentage (1.5%) relied solely on early reporting.[7] Data from the ADDM (Autism and developmental disabilities and monitoring) network reveals that ASD cases increased from 6.2 per 1,000 children born in 1994 to 27.6 per 1,000 children born in 2012.[4] The disorder's prevalence was seen to quadruple over the past 30 years.[8] Notable increase in ASD prevalence have been reported in certain Canadian regions. By 2010, the prevalence of ASD had reached 1 in 106 children in Prince Edward Island and 1 in 63 children in Southeastern Ontario, among 6 to 9 years old.[1] According to centre for disease control and prevention (CDC) data, 1 in 59 eight-year-old children had ASD in 2014, and 1 in 54

had it in 2016.[9] The prevalence of ASD in the US has shown a fluctuating trend. Between 2000 and 2008, the prevalence escalated from 6.7/1000 to 11.3/1000. After remaining relatively stable between 2010 and 2012, the prevalence increased again, reaching 16.8/1000 in 2014 and 18.5/1000 in 2016.[6,9] In 2021, the CDC reported that, in comparison to other years, the US autism rate in 2018 was 1 in 44 children.[10] However, prevalence of ASD was lower in age group of (3 to 4) years, possibly due to delayed detection of developmental issues in younger children.[8] According to 2024 reports, wealthy nations of Europe had the lowest incidence of autism. The lowest autism rates, at 69.3 per 10,000 or 1 in 144, were found in France. Portugal came next with 1 in 42, or 7.05 per 10,000.[10] Research highlights the disparity in ASD prevalence between males and females where males are more likely to have ASD. This may be due to differences in brain structure and function between individuals having variations in cortical thickness, amygdala volume, and functional connectivity.[6,5] Attention deficit/hyperactivity disorder and other developmental disorders are more prevalent in males than female with Autism.[5] In 1990s, ASD was more prevalent among white children. However, recent trends indicate that Black, Hispanic, and Asian/Pacific Islander children are now more likely to be diagnosed with ASD. Historically, Black and Hispanic children have faced delays in receiving ASD diagnoses compared to their white counterparts. Fortunately, recent evidence suggests that this gap is narrowing.[4] In 2010, non-Hispanic white children were 2.5 times more likely to receive an ASD diagnosis than non-Hispanic Black.[11] It is projected that about 2 million individuals in India may be impacted by ASD. In rural areas of India, the prevalence rate for those aged (1-18) years is 0.11. The percentage prevalence among those aged (1-15) years in urban areas is 0.09. According to a 2021 analysis of the South Asian population (Bangladesh, India and Sri Lanka) prevalence rate of ASD in the (0-17) years age group ranges from 0.09% to 1.07%.[12] Examining the Phenotypic concordance and discordance of monozygotic and dizygotic twin pair allows for examination of roles played by genetics and environment. A twin study demonstrated that the shared environment constitutes a significant cause of ASD.[2] Fraternal twins (dizygotic twins) have a concordance rate of 0-10%, while identical twins (monozygotic twins) have a prevalence of 70-90% for developing ASD.[13,14]

RISK FACTORS OF AUTISM

Both environmental and genetic factors contribute to ASD.[15]

Genetic factors

Multiple gene mutations maybe linked to ASD as follows:

FOXP2 (Forkhead box P2) gene

A point mutation in the FOXP2 was present in all impacted family members, suggesting that this gene is related to speech as well as language impairments associated with ASD.

ST7 (suppression of tumorigenecity) gene

It was proposed that autism may be linked to a long non-coding RNA known as ST7 overlapping transcript antisense 1-4 (ST7OT1-4), which controls the expression of ST7.

IMMP2L (Inner mitochondrial membrane protease like) gene

This gene deficit had behavioral impacts.

RELN (Reelin) gene

RELN anomalies causes abnormal signaling protein involvement in neuronal migration and neural connections.[16]

Methylenetetrahydrofolate reductase (MTFHR) gene

The body's capacity to convert folate to its active form is diminished by a variant of the MTHFR gene, which raises the incidence of autism, particularly in nations where food is not fortified with folate.[15]

Cadherin 8 (CDH8) gene

Mutations in this gene is less likely to cause autism.[17]

Epigenetic factors

Improper regulation of epigenetic genes can result in neurodevelopmental disorders such as DNA methylation being linked significantly to the etiology of ASD by combining environmental and genetic variables that effect neurodevelopmental processes.[2,16] Dysregulation of proteins that control histone modifications are associated with ASD.A reduction in linker histone H14, which is produced by the HIST1H1E gene from the histone cluster 1H1 family member is linked to characteristics of ASD and intellectual disabilities. When micro-RNA production is disrupted, neurodevelopmental problems result.[16]

Parental age

The development of abnormal behaviour and autistic traits might been linked to mothers stress levels.[2,1] Greater age of expectant mothers was identified as a likely factor raising the incidence of Autism along with age related DNA methylation alterations in sperm from older fathers.[2,16]

Fetal environment

Various environmental exposures during gestation such as changes in sex hormones, maternal obesity, can result in

hypertension, which may change foetal development and raise the offspring's risk of long-term vascular, cognitive, and mental consequences. Pregnancy related infections stimulate the mother's immune system, initiate cytokine signaling, cross the placenta and may have a variety of negative neurological insults causing persistent, severely aberrant cognitive and behavioral reactions.[2,18]

Sex steroids

The chance of getting ASD in offspring may be increased by high levels of testosterone, in the womb. This concept is related to male brain theory of autism, which holds that people with autism exhibit an excess of male brain characteristics.[2]

Maternal weight

Children born to mothers who were underweight and obese had a higher chance of developing ASD.[13]

Diabetes

Mothers with diabetes have a 62% higher incidence of ASD child than mothers without it.[2,3]

Nutrition

A mother's depletion of vital nutrients is linked to poor health outcomes for her children, including higher chance of autism due to deficiency of micronutrients like folic acid, zinc, vit D and omega 3.[13,1] Brain neurons and glial cells have active vit D receptors and enzymes, suggesting that vit D plays part in foetal neuro-development. Human body needs vit D for no. of biological processes, such as calcium homeostasis and metabolism. Chronic zinc shortage during pregnancy may result in neurodevelopment abnormalities in embryonic stage.[16]

Environmental factors

Heavy metals

Numerous body processes can be negatively impacted by heavy metal exposure, leading to neurological and behavioral dysfunction.[2] Lead and mercury are particularly lethal in genesis of autism.[1,2]

Pesticides

Pregnancy related exposure to organophosphates was linked to a 60% higher risk of ASD.[2] Higher chance of developing ASD and developmental delays was likely if pyrethroid insecticide exposed before/during 3rd trimester.[2,15]

Organic pollutants

Exposure to phthalates and bisphenol were found to adversely effect neurodevelopment in offspring.[2]

Potential characteristic features in ASD children comprises

Abnormalities in the limbic system

Smaller, densely packed neurons may contribute to social impairment and emotional regulation difficulties.

Cerebellar differences

Reduced numbers of Purkinje neurons may impact emotional processing, language, and motor coordination.

Increased glial cells

Elevated numbers of astrocytes and microglia in the cerebral cortex may influence neuronal function and immune responses.

Brain size variations

Early childhood macrocephaly (increased brain size) normalizes by mid-childhood, with regional variations in brain structure size.

Disrupted neuronal connections

Mutations in cell adhesion molecules, neuroligins, and anchoring proteins impair synaptic formation and maintenance.

Synaptic dysfunction

Loss-of-function mutations in genes essential for synapse development and function contribute to the ASD pathology.[19]

ETIO-PATHOGENESIS

Autism is multifactorial including abnormalities in synapse formation and function, impaired synaptic adaptability, disrupted neural circuitry, imbalance in the gut-brain axis, neuroinflammation and altered brain structure or connectivity.[19] The possible genetic mutations in autism seen to disrupt normal brain development and function, leading to diverse manifestations listed as follows:

SHANK3 gene mutations

Impairs synaptic signaling, leading to deficits in communication and social interactions characteristic of ASD.

PTEN gene

Mutations can result in excessive cell proliferation, contributing to macrocephaly observed in some ASD patients. PTEN influences neuronal function and synaptic plasticity affecting learning and behaviour.

DDX53 gene

DDX53 gene variants are primarily expressed in the brain and testis which likely elucidate higher prevalence of ASD in males.

Copy number variations (CNVs)

Involves deletions or duplications of genomic segments, potentially disrupting multiple genes. Such variations can affect genes responsible for cell adhesion, ion channels, scaffolding proteins, and signaling pathways like PTEN and mTOR (mammalian target of rapamycin), leading to synaptic dysfunction. Notable CNVs linked to an increased risk of neurodevelopmental disorders are 16p11.2 deletion/duplication (located on chromosome 16) and 22q11.2 deletion/duplication which can lead to physical and developmental issues.[20]

Usp9x gene

These mutations can disrupt protein stabilization for brain, development and learning.[21]

Genetic pathways associated in autism

Synaptic function and neurotransmission

The CNTNAP2 gene causes potassium channel clustering which leads to disruptions in synaptic function and imbalances in excitatory and inhibitory signaling.

Neurotransmitter system

Alteration in gamma-aminobutyric acid (GABA) receptors, affects inhibitory signalling in the brain. Mutations in genes like GABRB3 are linked to disrupted GABAergic transmission contributing to ASD symptoms.

Protein synthesis and degradation

Neuronal function relies on precise regulation of protein synthesis and degradation. Mutation of FMR1 (Fragile X syndrome) and UBE3A (Angelman syndrome) result in imbalances in protein homeostasis leading to synaptic dysfunction and altered neuronal plasticity.

Calcium signaling

Calcium is essential for various cellular processes, including neurotransmitter release and gene expression. Disruptions in calcium homeostasis by gene mutation can affect this pathway.[20]

Autistic individuals with brain deformities

Autistic individuals with brain deformities tend to experience accelerated brain growth immediately after birth, followed by normal or relatively slower growth during childhood. This unusual growth pattern is most prominent in the frontal and temporal lobes that are associated with higher cognitive specializations such as social cognition and language development.[19] Also individuals with widespread prefrontal dysfunction may struggle to control their movements in reaction to basic external cues which could be linked to their difficulty in regulating intricate social behaviour triggered by complex internal signals. There is overlap between cognitive and motor function as several areas controlled by prefrontal areas are not efficiently synced with one another.[22]

Synapse dysfunction

Characterized by disrupted synapse and dendrite spine growth. This disruption may be attributed to impaired neurexin-neuroligin cell-adhesion signaling or dysregulated synthesis of synaptic proteins. Research on functional connectivity in autistic brains has revealed both hypo-connectivity and hyper-connectivity. Hypo-connectivity is often observed in inter-hemispheric connections such as lower neuron density in the corpus callosum and cortico-cortical functional connectivity. Notably, the amygdala a structure involved in emotion regulation exhibits altered connectivity patterns in autistic individuals. The amygdala develops structural connectivity with the cortex by gestational week 13 and matures by 8 months. However, in autism rapid increase in amygdala size correlate with social interaction and communication deficits. Additionally, studies have found local over-connectivity in the cerebral cortex and weak functional connections between the frontal lobe and the rest of the cortex, highlighting the complex neural circuitry underlying autism. ASD individuals with left hemisphere dominance tend to exhibit preferential processing of information in the left hemisphere of the brain rather than in right. The left hemisphere is specialized for detail-oriented processing whereas right hemisphere is involved in global and integrated processing essential for pattern recognition. This left lateralization can impact various cognitive functions such as facial recognition where the brain tends to process visual information focusing on local details rather than the overall face leading to impaired facial recognition and spatial abilities.[19]

Cerebellum role in ASD

The cerebellum receives input from various brain regions, including motor, sensory and cognitive areas through mossy fiber inputs. These inputs are processed and then transmitted to different parts of the brain, influencing various functions such as sensorimotor, language, emotional regulation, and executive abilities. The cerebellum contains more than half of the brain's mature neurons and its circuits play a vital role in motor control. Excitatory inputs from mossy fibers and instructional signals from climbing fibers enable the cerebellum to refine motor skills and learn new behaviors. Disruptions in the cerebellum's structure and function can have a profound impact on behavioral and cognitive

development, particularly those involving mossy fibers and Purkinje cells contributing to development of the ASD.[23]

Immune system activation and neural connectivity in autism

Children with autism exhibit inflammation in both the peripheral and central immune systems, characterized by increased levels of pro-inflammatory cytokines and activation of microprocessing microglia.[19]

CLINICAL PRESENTATION IN AUTISM

As autism is a spectrum of disorders there is no one particular set of symptoms. Nearly every person who has been diagnosed displays a distinct set of their typical symptoms. Clinically the primary symptoms include little to no- eye contact, directional signaling through eye gaze during communication, and neutral faces in response to various emotional cues.[24] From parents' observations about their ASD children, they reported avoiding eye contact or feeling as though they were staring blankly.[25] Given below are the clinical features observed in ASD individuals.

Behavioural changes

Social

Isolation where ASD children of 18 months old had higher rates of challenges with motor skills and social communication.[26] It is from their incapacity to make new friends and consequently have fewer friends than their age-group counterparts.

Repetitive behaviours

Although toddlers are the primary focus of repetitive behaviours like spinning, back-and-forth running, adults can also exhibit these behaviours. In female children, the degree of repetitive behavior and restrictive/narrow interests is minimal.[24,27]

Anxiety symptoms

Trouble figuring out one's own feelings. Male and female autistic individuals seen to experience anxiety at the same levels. Studies show that 20%-42 % of teenagers with autism exhibit severe symptoms of anxiety and depression. People with autism experience more anxiety as they get older, from infancy to adolescence. Anxiety of some kind affects 40%–84% of children with autism.

Self-harm

Aggression, self-harming behaviour as well as intimidating conduct makes them vulnerable to the hurting themselves.

Short attention span

It is measured by infrared eye tracking. This suggests that people with autism have trouble focusing on one subject for a long time.[24] When their names are spoken majority of young autistic children do not reach out and appear to not pay attention or comprehend instructions.[27,28] This type of hypo responsive behaviour/poor reaction to environmental cues can originate from neural abnormalities in the early stages of sensory development.

Phobias

Such as a fear of darkness, thunderstorms, animals seen to co-occur.[24,29]

Hypersensitivity

Approximately 60%-96% of autistic children exhibit hypersensitivity issue to hearing in which they perceive certain noises far more intensely than typical people.

Selective eating habits

Autistic children are susceptible to nutritional deficits. To varying degrees, different food attributes contribute to food selectivity. Food texture accounts for 69%, appearance for 58%, taste for 45%, fragrance for 36%, and warmth for 22%. One factor contributing to food rejection is anxiety and sensory hyperactivity. Children with more serious cognitive problems develop a propensity of eating inedible objects like chalk and paper which causes them to have rumination issues. Indigestion, tooth damage, and intestinal blockage may be the outcomes of this.

Streamlined routine

Everyday tasks need to be carried out in same manner. For instance, they prefer to eat same foods, wear exact same attire every day and might get upset if routine is altered.

Curiosity

They might spend a large portion of their playing time inspecting the rotation of spinning objects, such as toy car tires or wheels or ceiling or pedestal fans.[24]

Head orientation

Toddlers with ASD struggle to keep their heads in the middle during attention processes.[26]

Physiological changes in ASD

Speech delay

Majority of autistic children are incapable of interacting through language and while some may have extremely limited speaking abilities.[24,27]

Gastrointestinal issues

Primarily constipation apart from nausea, vomiting, stomach-aches, diarrhoea are experienced. The likelihood of nausea issues observed was 11.2% higher in aggressive children.[30]

However, as people age, gastrointestinal symptoms continue to exist in them.[31]

Altered immune system

The immune system serves as a conduit between the central nervous system as well as the gut microbiota but these individuals exhibit impaired immune system regulation.

Neurological disorders

It is due to neurological issues and intellectual abnormalities disorder like epilepsy may co-occur.[24]

Sleep difficulty

Sleep disruptions like early or waking up frequently can result in daily tiredness which can be a warning indication in early years of autistic individuals.[24.29,30]

Early motor abnormalities

Standing, walking, jumping, running, poor balance coordination, toe walking, delayed eye blinking are caused by underdeveloped brain regions that link perception and movement in children with autism.[24,29]

They also are prone to have delayed acquisition of sitting without assistance, standing without assistance and walking alone.[26]

Insensitive to pain

Autistic individuals are insensitive to pain and occasionally may get headaches, particularly migraine. But they are photosensitive and show hyperactivity to light making them react painfully to bright light.

Co-occurring disorders

Personality and mood problems, schizophrenia and the obsessive-compulsive disorder have been associated to people with autism. The most common co-occurring disorder with autism spectrum disorder is compulsive disorder.[24]

Sensory characteristics

Children may exhibit unusual attention to environmental sensory characteristics such as obsession with lights or movement or smell of the objects.[28]

AUTISTIC INDIVIDUALS DEMONSTRATE EXISTENCE OF CERTAIN PHYSIOLOGICAL CHALLENGES

GI disturbances in autism

A significant proportion of individuals with autism, ranging from 46% to 84% experience gastrointestinal issues, including reflux, diarrhea, constipation, inflammatory bowel disease and food allergies.[19] The GI tract plays a crucial role in breaking down food particles into smaller molecules through digestion. These molecules then absorbed by the intestinal epithelium and transported into the bloodstream or lymphatic system through various transport mechanisms. The intestinal mucosa is constantly exposed to a vast array of foreign antigens and microorganisms from the environment. However, the intestinal barrier's regulatory mechanisms maintain mucosal immune function and prevent excessive inflammation. Despite the presence of gut flora, food antigens, and pathogens the mucosal immune system mounts a controlled physiologic inflammatory response that balances T helper 1 (Th1) and Th2 responses. Intestinal epithelial cells express major histocompatibility complex (MHC) molecules activating regulatory T cells (Tregs) and serving as non-professional antigen-presenting cells. The intestinal barrier comprises multiple components including epithelial cell integrity, mucus production, paracellular permeability and innate immunity. Dysregulation of these components can lead to inflammatory intestinal disorders. Escherichia coli can invade intestinal cells, altering actin dynamics, modulating immune responses and disrupting tight junctions. This compromise of the intestinal barrier leads to increased permeability and diarrhea. Conversely, interferon-beta (IFNβ) has been shown to protect the intestinal barrier whereas Tumor necrosis factor-alpha (TNF-α) disrupts it by inhibiting IFNβ. Certain microorganisms such as *Clostridium bolteae* have been found in the intestines ASD children that can exacerbate gastrointestinal symptoms.[32]

Desulfovibrio complications

Is a sulfate-reducing bacterium (SRB) observed in 50% autistic individuals. This anaerobic bacterium is resistant to penicillin, suggesting it may thrive following antibiotic treatment. It can metabolize sulfate and nitrate. While nitrate is toxic to other intestinal flora, such as methanogenic bacteria the relative tolerance of SRB to nitrate and nitrite suggests that nitrate may contribute to the proliferation of SRB in the gut. Elevated levels of nitrate and nitrite have been linked to childhood inflammatory bowel disease, which is also associated with an overgrowth of desulfovibrio. Notably, individuals with autism often exhibit excess plasma nitrate and nitrite, indicating a potential connection between SRB, nitrate, and autism. Laboratory studies have shown that when oligodendrocytes and astrocytes are exposed to nitric oxide (NO), neurons are more vulnerable to damage particularly their axons comprising the white matter

suggestive of excessive NO exposure may contribute to the white matter abnormalities often in autism.[33]

Immune system imbalances

The blood-brain barrier (BBB) plays a crucial role in maintaining brain homeostasis. However, in children with ASD the BBB's function is compromised due to neurological inflammation, immune dysregulation, and elevated inflammatory cytokines. The significantly leads to reduced CD4+ and CD8+ lymphocyte sub-populations, imbalance between Th1 and Th2 cytokines, altered interleukin (IL) and IFN-gamma levels with increased activation of Th1 and Th2 pathways and imbalanced immunoglobulins in serum.[32]

CONCLUSION

ASD exhibits significant heterogeneity due to intricate underlying patho-mechanisms activated by diverse causes. Some individuals with ASD may independently execute all daily living duties, whilst others necessitate considerable assistance for fundamental tasks. The causes of illness and pathogenic processes are still not fully understood.

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