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Understanding Autism Spectrum Disorder: An Overview

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Abstract: ***Autism spectrum disorder (ASD) includes neurodevelopmental disorders which show characteristic lack of social interaction, verbal and nonverbal communication. The distinguishing social behaviors include an avoidance of eye contact, issues with emotional control or issues in understanding the emotions of others, and a limitation of range of activities and interests. It is a complex multi factorial disorder resulting from the combination of genetic and environmental factors and that genetic susceptibility interacts with environmental factors in ASD etiology. Neuroimaging studies have led to the understanding of structural and functional abnormalities of the brain development in patients with ASD, pathological changes that occur in brain of patients with ASD and therefore the genetic bases of the brain development. The presentation and severity of symptoms significantly vary among individuals with ASD. It is important to identify the red flags and various signs as early as possible so as to ensure early interventions. The diagnosis of ASD is clinical based on the symptomatology, developmental history and behavior. The treatments include behavior and communication Approaches, dietary approaches, medication. Clinicians can make a difference by providing timely and individualized interventions. They play a crucial role in diagnosing ASDs consistent with clinical criteria through a comprehensive evaluation that has a thorough medical and developmental history, behavioral and play observations, and a review of standardized cognitive and language evaluations. Further research in proper investigations of etiologies and appropriate behavioral and educational interventions is needed to broaden the horizons on the understanding of ASD.***

1. Introduction

Autism spectrum disorder (ASD) includes neurodevelopmental disorders which show characteristic lack of social interaction, verbal and nonverbal communication. There have been changes in the diagnosis of ASD in the Diagnostic and Statistical Manual of Mental disorders (DSM-5) (American Psychiatric Association, 2013).One dimensional diagnosis (ASD) has been made by integrating several diagnoses which include

1) Persistent deficits in social communication and interaction
2) Limited, repetitive patterns of behavior, interests and activities.

The distinguishing social behaviors include an avoidance of eye contact, issues with emotional control or issues in understanding the emotions of others, and a limitation of range of activities and interests. Atypical language development is regarded as in co-existing condition. [1]

The term autism was first coined by a Swiss psychiatrist Paul Eugen Blueler in 1912 for defining the symptoms of Schizophrenia. [2] Leo Kanner first conceptualized autism when he reported about 11 children who had "an innate inability to form the usual, biologically provided affective contact with people" in 1943 and labeled it as early infantile autism. [3] Later in 1944, an Australian pediatrician Hans Asperger described a syndrome where he reported four boys having significant difficulties in social interaction and non verbal communication along with repetitive patterns of behavior and interests which is now called as Asperger syndrome. [4] Leo Kanner and Hans Asperger are the ones who designed the basis of modern conceptualization of autism.

The worldwide prevalence of ASD has rapidly increased over time, however, the etiology is been poorly understood.

The current prevalence of ASD in the latest large-scale surveys is about 1%~2% [5, 6] ASD occurs more often in boys than girls, male-to-female ratio being is 4:1. [7] The prevalence has been increasing worldwide over the past decades, from approximately 4 per 10 000 to 6 per 1000 children. [8, 9, 10, 11, 12] This increased prevalence is a result of increased public awareness, broadening of diagnostic concepts, improved detection and reclassifications of ASD. [7] [13] There is also an increase in unidentified risk factor(s) that causes ASD and therefore more research is needed to address this.

1.1 Etiology

ASD is a complex multi factorial disorder resulting from the combination of genetic and environmental factors. It is believed that ASD is a highly heritable disorder and that genetic susceptibility interacts with environmental factors in ASD etiology. Hence the interactions between genes and environmental factors is necessary. [14]

1.2 Genetic Factors

Genetic defects and chromosomal anomalies have been found in 10%~20% of individuals with ASD. [15, 16] Siblings born in families with ASD patients have a 50 times higher risk of ASD, with a recurrence rate of 5%~8%. [17] The occurrence of ASD in monozygotic twins is up to 82%~92% and 1%~10% in dizygotic twins. Prevalence of ASD are higher among individuals with various genetic disorders like fragile X syndrome and tuberous sclerosis. Advanced parental age may increase the chance of genetic mutations which happen spontaneously as genetic material is copied from parent to offspring. [18] Metabolic errors like phenylketonuria, creatine deficiency syndromes, adenylosuccinatelyase deficiency and metabolic purine disorders are also associated with 5% o f individuals with ASD [19] Recently, cerebellar developmental patterning gene ENGRAILED 2 in correlation to autism was reported [20]. It is the first genetic allele that contributes to ASD susceptibility in almost 40% of ASD patients. Other genes such as UBE3A locus, GABA system genes and serotonin transporter genes have also been considered as the genetic

factors for ASD. [16]

There have been remarkable advances in the knowledge of genetics of autism such as identification of specific alleles contributing to the autism spectrum has provided important pieces for the complexity of ASD. Genetic studies have shown that there are mutations that interfere with the neurodevelopment in utero. These abnormalities create a pattern of dysfunctional neural networks which are typically involved in the socioemotional processing. These sets of genes and their pathways which contribute towards formation, stabilization and maintenance of functional synapses are involved in ASD. These genetic aspects coupled with an in-depth phenotypic analysis of the cellular and behavioral characteristics are necessary to explain the etiopathogenesis of ASD. Also, electrophysiological studies show alterations in both resting-state and stimulus-induced oscillatory activities ASD patients. [21] Many genes have already been identified which have helped a lot in unraveling the pathogenesis and new therapeutic interventions. Yet a better understanding of role of genetics in ASD is needed. [22]

1.3 Environmental Factors

Along with genetic factors, many environmental factors have also been found to increase the risk of developing ASD. [23] Diverse environmental causal factors including prenatal, perinatal, and post natal factors also contribute to ASD. prenatal risk factors include exposures like maternal contact

ASD is more of a 'neural systems' condition that is mediated by abnormalities in regionally distributed cortical networks rather than separated brain regions. Therefore, ASD is also called as a 'developmental disconnection syndrome' [32]

2. Clinical Features

The presentation and severity of symptoms significantly widely among individuals with ASD. Early signs of ASD may be observed in an infant as early as 6 months.

Red Flags

- Do not response to their name by 12 months of age
- Do not point out at objects to show interest (pointing at an airplane flying over)
- Do not play “pretend” games (pretending to “feed” a doll) by 18 months
- Avoiding eye contact and wanting to be alone
- Having trouble in understanding other people’s feelings or touble talking about their own feelings
- Having delayed speech and language skills
- Repeating words or phrases again and again (echolalia)
- Giving unrelated answers to questions
- Getting upset by minor changes
- Having obsessive interests
- Flapping their hands or rocking their body or spinning in circles
- Having odd reactions to the way things sound, smell, taste, look, or feel

with high levels of air pollution, maternal viral and bacterial infections, exposure to teratogens like selective serotonin reuptake inhibitors, thalidomide, anticonvulsants such as valproic acid. [24, 25]

Perinatal factors are Birth complications involving birth asphyxia, Low birth weight, short gestation length [25] Post-natal factors associated with ASD include viral infections, hypoxia, autoimmune disease, mercury toxicity, and others. [24, 26, 27] Whereas, prenatal ingestion of vitamins during pregnancy and the months before pregnancy have been found to reduce the risk of ASD. [28]

1.4 Neuroimaging

Neuroimaging studies have led to the understanding of structural and functional abnormalities of the brain development in patients with ASD, pathological changes that occur in brain of patients with ASD and the genetic bases of the brain development. [29] Anatomical structure, the aspects of local neuronal circuitry and the functions of brain regions are affected by the synaptic deficits mediated by genetic factors in ASD. [30] The clinical variation of ASD phenotype may also be reflected on the level of brain structure and function. Hence, it is important to know the relationship between the structure, function and connectivity in the ASD brains. Neuroimaging allows us to directly examine the brain in vivo, and to probably facilitate the development of a more personalized approach in the treating ASD. [31]

Social Skills

Social issues are one of the most common symptoms in ASD. ASD patients do not have just social difficulties like shyness. The social issues they face cause serious problems in everyday life.

- Do not respond to name by 12 months of age
- Avoiding eye-contact
- Preferring to play alone
- Do not share interests with others
- Interacting only to achieve a desired goal
- Having flat or inappropriate facial expressions
- Do not understand personal space boundaries
- Avoiding or resists physical contact
- Not comforted by others during distress
- Having trouble understanding other people’s feelings or talking about own feelings

Communication

Each ASD patient has different communication skills. Some can speak well. few can’t speak at all or only little. About 40% of children with an ASD dont talk at all. About 25%–30% of children with ASD can speak some words by 12 to 18 months of age and then lose them. Others speak until later in childhood. [33]

- Repeating words or phrases again and again (echolalia)
- Delay in speech and language skills
- Reversing of pronouns (e.g., says “you” instead of “I”)
- Giving unrelated answers to questions
- Do not point or respond to pointing
- Using no or very little gestures (e.g., does not wave goodbye)
- Talking in a flat, robot-like, or in a singing-a-song voice

- Do not pretend in play (e.g., does not pretend to "feed" a doll)
- Do not understand jokes, sarcasm, or teasing

Unusual Interests and Behaviours

Few patients may show unusual interests and behaviors like:
- Playing with toys the same way every time
- Lining up toys or other objects
- Liking parts of objects (e.g., wheels)
- Being very organized
- Getting upset by minor changes
- Having obsessive interests
- Urges to follow certain routines
- Flapping hands or rocking body or spinning self in circles

Other Symptoms
- Impulsivity (acting without thinking)
- Hyperactivity (very active)
- Short attention span
- Aggression
- Causing self injury
- Temper tantrums
- Unusual eating and sleeping habits
- Unusual mood or emotional reactions
- Having a lack of fear or more fear than expected
- Odd reactions to the way things sound, smell, taste, look, or feel [34, 35]

3. Diagnosis

The diagnosis of ASD is clinical based on the symptomatology, developmental history and behavior. Earliest detection of signs and monitoring, screening and evaluation of development and developmental milestones help in diagnosis of ASD.ASD is generally detected by 18 months. The severity varies significantly among children with ASD. The typical age of onset is before 3 year and the typical core symptoms include qualitative impairments in social, language and communication skills, as well as repetitive interests and behaviors. However, these impairments can be subtle and may not be detected before school age. Many children do not receive a final diagnosis until they are adolescents or adults. This delay means that children with ASD won't get the early help they need.

The Checklist for Autism in Toddlers (CHAT), Modified-Checklist for Autism in Toddlers (M-CHAT), Childhood Autism Rating Scale (CARS) , Social Responsiveness Scale-Parent and Teacher (SRS) are some of the widely used structured instruments for screening of ASD in high-risk children for eg: siblings of autistic children, children with developmental delay, children with genetic syndromes, etc. [36, 37, 38, 39] Differential diagnosis includes childhood schizophrenia, learning disability, and deafness.

4. Treatment

ASDs are lifelong chronic disabilities. Currently, there is no cure for the core symptoms of autism.
The types of treatments are:
- Behavior and Communication Approaches
- Dietary Approaches
- Medication

Educational and behavioral treatments have been the mainstay of the management of ASD to improve the functioning of the affected child. These treatments may reduce symptoms, improve cognitive ability and daily living skills, and maximize the ability of the child to function and participate in the community. The focus is on developing language, social responsiveness, imitation skills, and appropriate behaviors. The ABA (Applied Behavior Analysis) is one such behavioral approach that involves teaching new behaviors by explicit reinforcement in which problematic behaviors are addressed by analyzing triggers in order to change factors in the environment that are contributing to that behavior.Another behavioral approach is TEACCH (Treatment and Education of Autistic and Related Communication Handicapped Children) that takes advantage of strengths in visual information processing using strategies like visual schedules, clearly structured and organized classrooms and structured learning activities that are broken down into manageable, visually organized steps. [40] These techniques should ideally begin early in the pre-school period and should be followed by highly individualized educational intervention in the school. [41, 42] Occupational therapy, social skills training. Speech therapy are also found to be effective. Most experts suggest that treatment of ASD should be highly individualized. Treatment of behavioral problems such as aggression, agitation, hyperactivity, inattention, irritability, repetitive and self-injurious behavior leads to a better overall treatment of ASD. [43]

Pharmacological treatments include typical antipsychotics, atypical antipsychotics, antidepressants, selective serotonin reuptake inhibitors, α2-adrenergic agonists, β-adrenergic antagonist, mood stabilizers, and anticonvulsants. [44, 45] As of now, there is no medication to improve social communication. [46] Choice of medical treatment highly depends on co existing psychiatric conditions like OCD, schizophrenia, mood disorders, intellectual disabilities and other physical and behavioral disorders. [47] Antidepressants and anti-psychotics are the most commonly used agents. [48]

There are several other options including opiate antagonist, immunotherapy, hormonal agents, megavitamins, dietary supplements. [43, 47]

However in some patients, symptoms remain refractory to pharmacological therapy. [49] This is because of severe progression of the disease and co morbidities which cause decreased quality of life. Deep Brain Stimulation is an alternative intervention for such patients who do not benefit from other treatments. It was approved by the FDA in 1997 and is used to send electrical impulses to specific parts of the brain. [50, 51]

5. Conclusion

ASD is a complex disorder characterized by impairments in three domains: communication, reciprocal social interaction and behaviors that are restricted and repetitive in nature. The etiologies include genetic and environmental factors.

Genetics and neuroscience have identified fascinating patterns of risk but without much practical benefit yet. Also, neuroimaging studies have led to the understanding of structural and functional abnormalities of the brain development in patients with ASD. It is important to identify the red flags and various signs as early as possible so as to ensure early interventions. The treatments include behavior and communication Approaches, dietary approaches, medication. Deep Brain Stimulation has also been tried in patients who do not benefit from other treatments. Considerable work is still needed to understand how and when behavioral and medical treatments can be effective and for which children. It is also important to implement what we already know and develop services for patients with autism spectrum disorder. Clinicians can make a difference by providing timely and individualized interventions. They play an crucial role in diagnosing ASDs consistent with clinical criteria through a comprehensive evaluation that includes a thorough medical and developmental history, behavioral and play observations, and a review of standardized cognitive and language evaluations. The key architecture of ASD development is still unknown which could be a target for treatment. Further research in proper investigations of etiologies and appropriate behavioral and educational interventions is needed to broaden the horizons on the understanding of ASD.

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