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Review

Asperger's Syndrome and Brain Mechanism: An Overview

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ABSTRACT

Asperger's syndrome (AS), a neurodevelopmental disorder and a form of autism spectrum disorder (ASD), is characterized by restricted interests, stereotypical behavior, and lack of delay in the development of language and cognitive abilities. One in every 44 children has ASD, which involves interactions between genetic and environmental factors. It is more common in men than women and has comorbidities. Since there is no treatment for ASD, curative approaches are used. This review provides information about AS as well as an overview of the genetic and environmental factors that contribute to it.

Keywords: Asperger's syndrome, autism spectrum disorder, environmental factor, genetic factor, neuropathology

Asperger's syndrome (AS), a form of autism spectrum disorder (ASD), is a neurological disorder characterized by restricted interests, stereotypical behaviors, and social communication difficulties.[1,2]

In 1944, Hans Asperger described individuals who had difficulties in communication and social interaction and could not establish physical and emotional bonds. In the following years, in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), this definition was evaluated under the title of pervasive developmental disorder not otherwise specified (PDD-NOS). Autism, AS, PDD-NOS, Rett syndrome, and childhood disintegrative disorder are in the category of PDD.[3-5] Since these disorders have become difficult to diagnose, the DSM-V has developed a new subcategory called ASD. Autism, AS and PDD-NOS are included in this group.[6]

Asperger's syndrome is differentiated from ASD in the restricted area of interest, such as limited interests, stereotypical behaviors, impaired social communication, and a lack of regression in the development of characterized language skills and cognitive abilities. While the clinical diagnosis of AS is eleven years and older, this period in ASD is five years on average.[7]

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Comorbidities are common in patients with ASD, which complicates the diagnosis and treatment process.[8] The heritability in ASD is around 80%. Despite this heritability, environmental factors have a large share in the emergence of ASD.[9]

Asperger's syndrome is ten times more common in men than women. They have no cure and cannot be prevented, but there is evidence that early detection and intervention can greatly improve treatment.[10,11]

EPIDEMIOLOGY

An accurate estimate is uncertain as the diagnosis of AS is placed in the ASD category in the DSM-V. According to the estimations of the Centers for Disease Control and Prevention and the Autism and Developmental Disabilities Monitoring Network, ASD is approximately detected in one out of every 44 children. Autism spectrum disorder has been documented to affect every ethnic, cultural, and socioeconomic group, and it is four times more common in boys than in girls.[12] The prevalence of ASD is increasing yearly, through the improvement in diagnostic tools and changing diagnostic criteria.[13]

PATHOGENESIS

The exact cause of neurodevelopmental disorders, such as ASD, is unknown but considered a multifactorial disorder involving epigenetic interactions between genetic and environmental factors that affect mitochondrial function, neuroinflammation, and oxidative stress.[14,15]

Genetic

It is known that different genes are effective in the development of AS, a subtype of ASD. Genetic variations in gamma-aminobutyric acid receptor subunit beta-3 genes, which are associated with individual differences in empathy, are believed to be effective in the development of AS and ASD.[16,17]

In a study, it was found that AS harbors genetic risk factors overlapping with ASD and also has genetic risk factors specific to the AS phenotype.[18] In another study, mutations in the aryl hydrocarbon receptor nuclear translocator 2 gene were observed in both AS and ASD patients.[19]

Phelan-McDermid syndrome, which is located on chromosome 22q13.3 of the SH3 and multiple ankyrin repeat domains 3 gene and is caused by haploinsufficiency, is characterized by a speech disorder, intellectual disability, and autistic symptoms. Duplications occurring in the same region are associated with AS and phenotypes of hyperkinetic neuropsychiatric disorder.[20,21]

One of the reasons for the emergence of ASD is single gene mutations that occur as nova mutations with the effect of gene copy number variants (CNVs) and single nucleotide polymorphisms also contribute to the pathogenesis of ASD. Mutations that occur here affect the formation, transmission, and plasticity of synapses.[9,22] In about 9% of patients with ASD, CNVs with DNA deletions and duplications that alter gene function are identified.[23]

Abnormalities of the hippocampus, cerebellum, frontal cortex, and amygdaloid nucleus have been observed in different parts of the brain.[24] Individuals with genetic or chromosomal diseases such as Down syndrome or fragile X syndrome have an increased risk of ASD.[25,26]

Environmental Factors

Environmental factors are increasingly recognized as risk factors for the development of ASD.[27] They may affect already existing genetic factors in individuals with genetic predisposition or act as an independent risk factor.[23]

Conditions such as parental age, gastrointestinal problems, prenatal exposures, perinatal risk factors, smoking and alcohol use, vaccination, and maternal nutrition can be considered environmental factors that may cause ASD. Both maternal and paternal age is associated with the risk of having a child with ASD.[28]

Perinatal factors such as sex hormone alteration, preterm birth, maternal obesity, diabetes, infections, and *in vitro* fertilization are associated with increased risk factors for ASD.[23,29,30] Toxic metals are another factor in the development of ASD. One study showed that ASD patients had higher levels of mercury and lead in their blood and higher levels of cadmium, lead, and antimony in their hair.[31]

A study with pesticides showed that exposure to organophosphates during pregnancy increased the risk of ASD by 60%.[32] The nutritional status of the mother during pregnancy is also an important factor for ASD. A lack of essential nutrients in the mother increases the risk of infants with ASD.[33]

Mitochondrial Dysfunction

Mitochondrial dysfunction is the phenotypic feature of 80% of patients with ASD. Since mitochondrial homeostasis is important for both the development and function of the brain and the metabolism in neurons, a disorder that occurs here is an important risk factor for ASD.[34]

Since mitochondria are involved in vital functions such as cellular energy source, homeostasis, regulation of cell apoptosis, production of reactive oxygen species, ion metabolism, and controlling energy metabolism. In addition, even a small change could cause serious damage to neuronal function which has an impact on their development.[35-37]

Neuropathology

Brain abnormalities were observed in the brains of patients with ASD who were examined after death, in regions such as the hippocampal formation, amygdala, basal ganglia, thalamus, brain stem, cerebellum, limbic system, and cerebral neocortex. However, developmental brain abnormalities such as dysplasia, altered neurogenesis, and abnormal neuronal migration have been observed, which mostly occur during prenatal brain development. Decreased number of Purkinje cells in the cerebellum, which is associated with factors such as seizures, drugs, or near-death experience, which is highly likely to occur after birth, is one of the neuropathological factors associated with ASD formation.[38,23]

Comorbidities

The most common comorbidities in ASD are major depressive disorder (MDD), anxiety, attention-deficit hyperactivity disorder (ADHD), schizophrenia (SCZ), and obsessive-compulsive disorder (OCD).[39-41] Since AS has a greater number of common variations than subtypes of ASD, a genetic overlap of AS with ADHD, MDD, or SCZ is more consistent than with subtypes.[42,43]

Asperger's Syndrome is difficult to diagnose and is thought to be due to its high association with other comorbidities. The DSM-IV diagnostic criteria are used since there is no specific diagnostic method to define comorbidities in patients with AS.[44]

Anxiety is one of the most common comorbidities in ASD. It is found in 40% of patients with ASD.[45] Specific phobias, generalized anxiety disorder, separation anxiety disorder, and social phobia are the most common anxiety disorders in ASD patients, and social anxiety is the most common. Depression, which is common in adolescents and adults with ASD, varies between 12% and 33% depending on age, gender, and social skills, and is a psychological comorbidity that is difficult to diagnose.[23] Obsessive-compulsive disorder, which is characterized by repetitive and disturbing thoughts and behaviors, begins in childhood and adolescence and its prevalence ranges from 2.6% to 37.2%. Diagnosis is difficult because of the great similarity between OCD and ASD, such as stereotypical behavior and strict adherence to rituals. However, it was found that children with ASD exhibited more saving and hoarding behavior.[46]

Individuals with OCD can be distinguished from ASD in terms of poor social skills, emotional behavior, ability to remember the direction of an object, and intense intellectual interests.[47] Half of the children with ASD may meet the diagnostic criteria for ADHD, characterized by symptoms of inattention, hyperactivity, and impulsivity.[23,48] About three-quarters of children suffering from ASD suffer from an additional illness. It is known that the diagnosis and treatment of these comorbid diseases for the correct diagnosis and treatment are important for the diagnosis and treatment of ASD.[49]

TREATMENT METHODS

There is no cure for ASD, therefore, treatment aims at activities that improve the quality of life such as reducing symptoms, improving patients' abilities in the line with their physical and personal characteristics, as well as minimizing basic deficiencies, and reducing problematic behaviors that limit their vital tasks. Individuals with ASD are unique, so a personalized treatment plan is made and treatment strategies are determined according to the patient's age, weaknesses, and strengths.[23]

Behavioral Interventions

In this method, which is based on the principles of applied behavior analysis, patients are monitored and supervised from an early age. It is a personalized behavioral intervention program designed to reduce the patient's undesirable behaviors, develop simple skills, improve social skills and enable them to use them more effectively with the applied behavior analysis program.[50,23] It is known that the treatment works and positive progress have been made in terms of behavior in patients.[51]

Educational Interventions

It is known that children with ASD need a special and personalized education plan. Verbal and non-verbal communication is planned according to the age, and social and behavioral abilities of the patient, which will focus on behavioral abilities and improve academic and social skills. It consists of two classroom-based models, which include the Learning Experiences and Alternative Programs for Preschoolers and Their Parents and the Treatment and Education of Autistic and related Communication Handicapped Children program.[51,52]

Speech and Language Therapy

Speech and language therapy aim to reduce and eliminate the language and communication difficulties of patients with ASD. For this purpose, Augmentative and Alternative Communication, which uses pictures or technology to overcome language and communication difficulties, is the most appropriate method for the patient, such as sign language, Picture Exchange Communication System, iPads, and speech output devices. and efforts are made to strengthen communication skills.[52]

Developmental Therapies

Developmental interventions not only improve language and speech skills, but also provide appropriate responses when communicating with others, engage in activities that improve the quality of communication, and encourage social communication with others. To realize this incentive, techniques such as modeling words and actions, giving meaning, and imitation are used as a daily routine.[52,53]

Pharmacological Applications

Risperidone and aripiprazole, which are binding dopamine and serotonin receptors, are used in the short-term symptomatic treatment of irritability including aggression, self-harm, and other destructive behaviors in ASD patients. Side effects occur in long-term use.[54]

Nutrition Therapy

It is known that patients with ASD experience more digestive problems and metabolic imbalances than normal people. Nutritional metabolism is thought to affect the behavior of children with ASD. For this reason, various diet programs are applied to reduce symptoms. One of these diets is a gluten-free and casein-free diet, in which both gluten and casein are removed from the diet of children with ASD.[55]

It is known that removing gluten and casein from the diets of patients with ASD reduces digestive disorders, behavior, and symptoms. The ketonic diet, which includes high fat, low carbohydrate, and appropriate protein amount, is another form of nutrition used in people with ASD, especially epilepsy patients.[55,56] Different types of nutrition are also preferred, such as yeast-free diets, and dairy-free diets.[57]

In conclusion, there is no cure for ASD, and there are several environmental and genetic factors that contribute to its pathogenesis. Current treatment methods alleviate the symptoms of the disorder and provide control of comorbid diseases. Appropriate treatment and methods are needed to investigate and prevent the causes of the disorder in more detail.

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