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A Systematic Review on Autism in Paediatric

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ABSTRACT:

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in social communication, behavior, and restricted interests. The severity and manifestation of ASD vary greatly among individuals, which is why it is referred to as a "spectrum." While the exact causes of ASD remain unclear, both genetic as well as environmental factors are believed to play a role in its development. ASD commonly presents in early childhood with symptoms such as social skill deficits, communication challenges, and repetitive behaviors. Comorbidities, including ADHD, anxiety, and epilepsy, are frequently observed in individuals with ASD, further complicating diagnosis and treatment. Due to the lack of definitive diagnostic tests, such as a blood test, the primary approach to managing ASD involves behavioral therapies, though pharmacological treatments like antipsychotics, SSRIs, and stimulants are sometimes used to address specific symptoms. Despite the availability of various medications, there is no cure for ASD, and treatments largely aim to alleviate symptoms and improve quality of life. Emerging research on genetic testing and neuroimaging may offer new insights into early diagnosis and targeted therapies. This review explores the clinical features, diagnostic challenges, and current management strategies for ASD, emphasizing the importance of a multifaceted approach to treatment that combines medication and behavioral interventions to address the disorder's complex symptoms.

Keywords: Autism Spectrum Disorder, neurodevelopmental disorder, behavioral therapies, pharmacological treatments.

Introduction

Three primary impairments define autism spectrum disorder (ASD), a neurodevelopmental disorder: limited, repetitive, and stereotypical behavior patterns; impaired speech; and impaired reciprocal social interaction. ASD-related medical comorbidities, symptom severity, and presentation heterogeneity are all referred to as spectrum. Attention-deficit/hyperactivity disorder (ADHD), anxiety, depression, epilepsy, metabolic, immunological, and digestive diseases are among the most prevalent underlying medical conditions. Pharmacological management of ASD is still difficult at the moment since there is no reliable and objective way to diagnose the disorder, such as by a blood test.

The primary treatment for the disease is usually behavioral therapies because there are no approved drugs to address its primary symptoms. Aripiprazole, risperidone, and haloperidol for irritability and aggression; methylphenidate, atomoxetine, clonidine, and guanfacine for ADHD; and melatonin for sleep disturbances are among the psychotropic medications with various mechanisms of action that have also been approved to lessen related symptoms and comorbidities. It often manifests between the ages of 18 and 36 months, and little is known about the biological processes that underlie it because the disorder's genesis is unclear. Additionally, ASD manifests as a variety of symptoms or comorbidities that vary in severity of impairment, impacting people at different stages of their lives.[1]

Comorbid conditions such tic disorder, obsessive-compulsive disorder (OCD), depression, attention-deficit hyperactivity disorder (ADHD), anxiety disorders, and intellectual disabilities are often linked to ASD. From the standpoint of epidemiology, a survey of research conducted since 2000 indicates that the prevalence of ASD is roughly 66/10 000, or 1/152 children, with a 5:1 male-to-female ratio.

Numerous studies have suggested that both genetic factors and environmental influences may play a role in the pathophysiology of ASD, although the exact mechanisms are not yet understood. However, research indicates that targeted behavioral therapies, pharmacological treatments, or a combination of medication and behavioral approaches can effectively address social communication deficits and associated symptoms. The Autism Diagnostic Observation Schedule (ADOS) can assess difficulties in social communication and other symptoms of ASD, but there have been few clinical trials that utilize it to demonstrate meaningful clinical improvements.[2]

Definition

The broad category of neurodevelopmental diseases known as autism spectrum disorders (ASD) has an impact on a person's behaviour patterns, social interactions, and communication abilities. From minor social impairments to severe communication and behavioural issues, the features of ASD differ greatly from person to person, which is why the term "spectrum" is used. Research indicates that both genetic and environmental variables are important in the development of ASD, even if the precise causes are not entirely understood.[3]

There are many misconceptions and mysteries surrounding autism spectrum disorder (ASD), a complicated neurodevelopmental condition that has long-lasting effects and is currently erupting as a global epidemic. It is typified by symptoms that limit and interfere with day-to-day functioning, restricted and repetitive behaviors, hobbies, or activities, and persistent impairments in social communication and interaction across settings. It also starts in the early developmental period.[4]

Characteristics of ASD

Social Interaction Challenges

Social connections are frequently quite challenging for people with ASD. These challenges could include trouble keeping eye contact and facial expressions, adjusting to social norms and expectations, and comprehending the intentions and feelings of others. People with ASD could find it difficult to make and keep friends, they might not comprehend that social interactions are two-way, or they might feel awkward sharing their hobbies and interests.

Communication Disorders

Another fundamental characteristic of ASD is communication impairments. Delays in language development, such as difficulties pronouncing simple sentences or first words, may be one way this shows up. There are some people with ASD who may not speak at all. People with ASD may struggle to express their needs, wants, or feelings through words in conversations, even if they have adequate language skills. Furthermore, nonverbal communication—including the comprehension and use of facial expressions and body language—may also be impacted.

Repetitive Behaviors and Interests

People with ASD frequently exhibit limited, repetitive interests and behavior patterns. These could include an excessive dependence on daily routines, repetitive physical movements (such clapping or rocking), and a strong focus on particular subjects or activities. Some people view these repetitive actions as a form of self-soothing or as an effort to exert control over an environment that otherwise feels unpredictably chaotic and overpowering.

Sensory Sensitivity

Many people with ASD have sensory processing disorders, which can cause them to react to light, sound, touch, taste, or smell very strongly or slowly. For instance, some people with ASD might not perceive pain or other body sensations, or they could find background noises in their daily surroundings unusually harsh.[3]

ETIOLOGY

ASDs are highly heritable neurodevelopmental diseases with a biological basis. Even so, the precise cause is still a mystery. Due to phenotypic variety and genetic complexity, determining the reason has proven to be difficult. Many genes are involved in ASDs, which are complex heritable illnesses with wide phenotypic heterogeneity. According to family studies of idiopathic ASDs, the likelihood of recurrence is estimated to be between 5% and 6% (range: 2%–8%) when an older sibling has an ASD, and even higher if there are already two children in the family with ASDs.[5]

Among the neurogenetic syndromes that appear to contribute to or are somehow linked to ASDs are, but are not exclusive to:

Fragile X syndrome: -The most prevalent hereditary cause of AD and MR in boys is known to be fragile X syndrome. MR, macrocephaly, huge pinnae, large testicles (especially after puberty), hypotonia, and joint hyperextensibility are among the phenotypes. Because the diagnosis affects other family members, it is crucial to identify a patient with fragile X syndrome for the purposes of genetic counseling. The etiologic yield of fragile X syndrome–DNA testing has varied from 0% to 8%, with a median of roughly 3% to 4%, depending on the prevalence of concomitant MR among research participants with ASD. However, between 30 and 50 percent of people with genetically proven fragile X syndrome will exhibit some traits of ASDs.

Neurocutaneous disorders: Tuberous sclerosis is characterized by fibroangiomata, kidney lesions, central nervous system hamartomas, seizures, MR, hypopigmented macules (which in young children may require a Wood's lamp examination to see), and behaviors that resemble autism and/or attention-deficit/hyperactivity disorder (ADHD). The majority of cases are novel mutations, even though tuberous sclerosis is a dominant disorder (with genes at 9q and 16p). Neurofibromatosis is the most prevalent neurocutaneous condition, yet it is less frequently linked to ASDs.

Phenylketonuria: Due to neonatal screening and nutritional management, phenylketonuria is currently a rare cause of ASDs and MR in the United States. Fetal alcohol syndrome : Children who are exposed to alcohol during gestation have an increased risk of ASDs in addition to other neurodevelopmental disorders.

Angelman syndrome: -The loss of the maternally expressed ubiquitin-protein ligase gene (UBE3A) on 15q due to deletion, paternal uniparental disomy, or imprinting mistakes is known as Angelman syndrome. Children with Angelman syndrome exhibit wide-based ataxic gait, seizures, increasing stiffness, hypotonia in early childhood, and GDD (and frequently are nonverbal)

Rett syndrome: - All girls who exhibit regression similar to autism should be evaluated for Rett syndrome, which typically manifests as a classic phenotype, particularly if they have microcephaly, seizures, and hand-wringing stereotypes. Males have a substantially lower prevalence of Rett syndrome and a more diverse appearance. Some guys with concomitant Klinefelter syndrome (having a normal number of sex chromosomes) exhibit more symptoms, while others die in infancy from neonatal encephalopathy.

Environmental Issues

Whatever the method, there is strong evidence that the majority of ASD cases are caused by interacting genetic variables, according to a review of research done in the last 50 years. However, environmental influences may have an impact on how the autism gene or genes are expressed. These elements might be a "second-hit" phenomena that mostly happens during fetal brain development, though they are still being studied. In other words, pre-existing genetic components that produce ASDs in certain infants may be modified by environmental factors.

Prenatal Period

Since many of the developmental brain defects known to be associated with ASDs occur during the first and second trimesters of pregnancy, environmental factors, including teratogens like thalidomide and valproic acid, are more likely to affect the fetus through maternal factors. Maternal sickness during pregnancy, such as rubella, may be a contributing factor. Recently, researchers looked into the potential link between embryonic testosterone levels and specific autistic traits, like restricted interests and aberrant social relationships at age 4.

Perinatal Period

There have also been studies on the effects of birth weight, gestational age, and conditions around the time of birth, but the findings have been mixed. It was recently discovered that there was a strong correlation between children who were later diagnosed with ASD and term neonatal encephalopathy. According to Badawi et al., 5% of newborn encephalopathy survivors received an ASD diagnosis, which is nearly six times higher than the rate for matched controls. This increase could be the result of an independent mechanism or a genetically acquired propensity that leaves the infants susceptible to both encephalopathy and ASD.

Postnatal Period

There have been suggestions of etiologic possibilities that take place after birth, specifically the measles-mumps-rubella (MMR) vaccine and vaccines that include mercury. After reviewing epidemiologic population-based data in 2001, the Institute of Medicine came to the conclusion that there was no proof linking the MMR vaccine to autism. Studies that have examined the relationship between the MMR vaccine and autism following the publication of that review have supported this conclusion

CLINICAL SIGNS

Social Skills Deficits

Social deficiencies that manifest during the first two years of life are more precise than language deficits, although they are frequently overlooked by parents. Social relatedness, which is the innate need to connect with people and share comparable emotional states, is universally lacking in children with ASDs. Children with ASDs are content to be alone, disregard their parents' requests for attention, and hardly ever make eye contact or utilize gestures or vocalizations to attract attention from others. They could have few, if any, friends later in life and find it difficult to empathize with others in social settings and cooperative activities.

Communication Deficits

Though this may alter as parents become more conscious of social milestones, the majority of children who are subsequently diagnosed with AD and PPD-NOS arrive to their PCP with "speech delay." As said before, by the time the child is 18 months old, the majority of parents feel that something is off. Lack of speech has been regarded as a defining characteristic of AD, particularly when it is linked to a lack of motivation to communicate and a lack of compensatory nonverbal cues like gestures. Children with less severe symptoms, particularly those with typical cognitive abilities, might be able to speak to some extent. Their speech might not be fluent or functional, and it might not be intended to communicate.

Regression

Between the ages of 15 and 24 months, between 25% and 30% of children with ASDs start to speak but eventually cease. Children with ASDs may also have a decline in their social skills (such as eye contact and responding to praise) and gestural communication (such as wave, point, etc.), or both. Atypical development, such as an abnormally high interest in objects or other nonsocial stimuli during the first year of life, or modest preexisting developmental impairments may be layered on top of regression, which can occur gradually or abruptly.

Asperger Syndrome

Until preschool or early school age, when their failure to form friendships becomes a worry, children with AS may have mild or limited speaking and go unnoticed. Language development is typically atypical, despite the fact that it is sometimes overlooked. When it comes to a particular topic of interest, children with AS are frequently highly talkative, but they struggle to articulate basic emotions or understand the thoughts and feelings of others. Fluent speech may be restricted to a small number of subjects, usually those in which the kid has a keen and intense interest.

Play Skills

ASDs are characterized by persistent sensory-motor and/or ritualistic play, as well as a lack of pretend play skills or a marked delay in them. The sensory-motor play stage may be the last one that some kids with severe ASDs ever reach. They manipulate things, mouth, whirl, and bang in a ritualistic or stereotypical way. Children with ASDs frequently engage in repetitive play that lacks imagination and mimicry. Common instances include lining up or spinning the wheels of automobiles rather of "driving" them, arranging crayons rather than drawing with them, or repeatedly stacking blocks in the same order.[5]

DIAGNOSIS

Neuroimaging

In order to better understand the scientific underpinnings of ASD, researchers are using non-invasive neuroimaging techniques to examine alterations in brain structure and function. These methods include positron emission tomography (PET), diffusion tensor imaging (DTI), structural magnetic resonance imaging (sMRI), and functional magnetic resonance imaging (fMRI). Researchers can see structural and functional variations in particular brain networks and areas in people with ASD thanks to these neuroimaging techniques. For instance, fMRI can show how the brain works when doing particular activities, which can assist identify how people with ASD struggle with social, linguistic, and cognitive skills.

Neuropathologic analyses of brain tissue from individuals with autism have identified a number of abnormalities, such as:

- Decreased numbers of Purkinje cells in the cerebellum
- Abnormal maturation of the forebrain limbic system, including decreased neuronal size, increased cell-packing density, and decreased complexity of the neuropil (i.e., the complex net of axonal, dendritic, and glial branching in which the nerve cell is embedded)
- Abnormalities in the cortical Mini columns in the frontal and temporal lobes, which are more numerous, smaller, and less compact in their cellular configuration and show decreased neuropil space in the periphery
- Developmental changes in the number and size of cells in the nucleus of the diagonal band of Broca, deep cerebellar nuclei, and inferior olive; and brainstem abnormalities and neocortical malformations [5]

Genetic testing

By examining genetic variations in a person's DNA, genetic testing for ASD can reveal risks related to the disorder. This test searches for particular genetic variations that have been connected by science to the onset of ASD. Variants in particular genes have been found to significantly affect the risk of ASD, despite the fact that the genetic background of ASD is incredibly complicated, involving several genes and the interplay of genes with environmental factors. For instance, Phelan-McDermid syndrome is linked to variations in the SHANK3 gene, and individuals with this syndrome frequently have characteristics of ASD. Fragile X syndrome, the most prevalent single-gene etiology of ASD known to be linked to ASD, is caused by variations in the FMR1 gene. Rett syndrome has been linked to mutations in the MECP2 gene, and individuals with Rett syndrome frequently have ASD.

Early screening methods

Analyzing children's behavioral videos and biomarkers using machine learning and artificial intelligence (AI) is one noteworthy new strategy. These technologies can assist researchers and doctors in identifying possible symptoms of ASD sooner by teaching computers to recognize particular behavioral patterns and physiological signals linked to the disorder. Eye-tracking technology, which evaluates children's social and cognitive development by examining their eye movement patterns while watching images or videos, is another innovative field. Research has demonstrated that when children with ASD encounter social scenes, their eye movements differ from those of typically developing youngsters. This offers a non-invasive window for early screening.[3]

Different tools used for diagnosing severity of ASD

To further elucidate the symptomatology and severity of the child's autistic features, standardized research assessment tools are utilized, particularly the Autism Behavior Checklist (ABC), Autism Diagnostic Observation Schedule (ADOS), Autism Diagnostic Interview-Revised (ADI-R), Autism Treatment Evaluation Checklist (ATEC), and Childhood Autism Rating Scale (CARS). ADOS and ADI-R are regarded as the gold standards for autistic children in the western world. However, the INDT test and the DSMV criteria for ASD can be utilized to diagnose ASD in developing nations with high sensitivity and specificity.[4]

Treatment

Treatments for aggression and irritability

Typical and Atypical antipsychotics have been used to treat it and the salient points will be described here.

Typical Antipsychotics

Haloperidol

One of the earliest drugs investigated for treatment in autism spectrum condition was haloperidol. Research on the effects of acute haloperidol administration has demonstrated improvements in hyperactivity, temper tantrums, withdrawal, stereotyped behaviors, and learning on discrimination tests. The daily doses employed in these investigations varied from 0.25 mg to 4 mg. Acute dystonic responses, agitation, and drowsiness were the most often reported adverse effects.

Antidepressants

Because autism spectrum disorder is characterized by repetitive, ritualistic activities and an emphasis on limited patterns of routines, antidepressants have been evaluated for use in treating this condition. Patients with autism spectrum disorders have been investigated using tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and other antidepressants.

Selective Serotonin Reuptake Inhibitors (SSRIs)

The effectiveness of SSRIs in treating autism spectrum disorder has been the subject of conflicting research. When these drugs are used in this patient population, some studies indicate no improvement and serious side effects, while other research reveal possible benefits in treating agitation and repetitive motions. In a 10-week open-label study, 28 kids and teenagers (ages 6 to 17) with common developmental problems participated to test the effectiveness of escitalopram.78 Irritability and general improvement scores showed significant improvement, and the study emphasized the importance of starting with very low doses and titrating gradually. Twenty-five percent of participants did not tolerate doses at or above 10 mg, and they responded to doses less than 10 mg. The most frequently reported side effects were hyperactivity and agitation.

Atypical antipsychotics

Risperidone

Risperidone is an atypical antipsychotic. Risperidone proved effective in lowering hyperactivity and aggression in autistic children as early as two years old, while also improving social responsiveness and global functioning, according to results on the Children's Global Assessment Scale (CGAS) and Childhood Autism Rating Scale (CARS). A Cochrane study suggests that risperidone may help reduce social disengagement, repetitive behaviors, and irritability in individuals with ASD. However, the authors stressed that the lack of a standardized end measure and the small sample sizes make it impossible to draw meaningful conclusions, therefore the analysis's findings should be viewed with caution.

Aripiprazole

It has been demonstrated that aripiprazole, at doses ranging from 5 to 15 mg/day for eight weeks, is safe, effective, and well-tolerated in lowering irritability in children and adolescents with autism who were displaying violent, tantrum-prone, or self-harming behavior. When compared to children who got a placebo, children who received aripiprazole demonstrated an average improvement of 6.17 points on the ABC irritability subscale, 7.93 points on the hyperactivity subscale, and 2.66 points on the stereotypy subscale, according a Cochrane analysis. The authors also noted that further investigation is required to gain a better understanding of aripiprazole's long-term safety, tolerability, and efficacy.

Risperidone and aripiprazole

Risperidone and aripiprazole have been licensed by the US Food and Drug Administration to treat irritability associated with ASD. However, to the best of our knowledge, just one published study directly compares the two drugs side by side. The change in ABC scores served as the primary end measure, and the findings showed that risperidone and aripiprazole shared comparable efficacy, safety, and tolerability traits. Other unconventional antipsychotics

Metabolic syndrome

Young people's use of antipsychotics is closely linked to metabolic syndrome, which includes type II diabetes, weight gain, and dyslipidemia. Almandil et al. (2013) found that aripiprazole, risperidone, and olanzapine were all associated with weight gain in children and adolescents. Additionally, Bobo et al. (2013) found that children and adolescents who received antipsychotics were more likely to develop type II diabetes. As each atypical antipsychotic has a distinct safety and tolerability profile, it is recommended that metabolic syndrome-related side effects be regularly monitored to inform treatment strategies. Research into wearable technology for remote physiological monitoring of heart function and internet-based monitoring of side effects is required because to the long-term negative effects of psychotropic-induced weight gain and metabolic syndrome.

Low dose venlafaxine was reported to be beneficial for repetitive behaviors and limited interests, social deficits, communication and language skills, inattention, and hyperactivity in a retrospective, open clinical report of ten people with autism spectrum disorder, ages three to twenty-one. Polyuria, inattention, nausea, and behavioral activation were among the side effects.[4]

Treatment for inattention and hyperactivity

Methylphenidate

Large open-label clinical studies comparing stimulant treatment (mainly methylphenidate) demonstrated good symptom reduction in both groups of children and adolescents with ADHD and those with ADHD and ASD. Using the Conners Rating Scale – Short Version parent/teacher ADHD index at 16 weeks as the primary outcome measure, a large double-blind, placebo-controlled experiment found that some children reacted well to optimal dose with methylphenidate. A secondary assessment of RUPP Autism Network data found that methylphenidate enhanced social communication and self-regulation in 33 children with PDD and hyperactivity. These results suggest that the dosage of methylphenidate is linked to changes in joint attention (social behavior regulation), with lower dosages being better than higher ones. If the goal is hyperactivity, then higher dosages are most likely needed.

Amphetamines

Although amphetamines have been used to treat ADHD in children, there is no published data on their efficacy in treating children and adolescents with ASD. The therapeutically useless pro-drug lisdexamfetamine dimesylate is created when D-amphetamine is joined to the amino acid lysine. The primary outcome measure, the investigator-rated ADHD Rating Scale IV (ADHD-RS-IV), indicated that lisdexamfetamine dimesylate was well tolerated and effective in treating ADHD in children and adolescents aged 6–17 years (Reference Coghill, Banaschewski, and LecendreuxCoghill 2013). Lisdexamfetamine dimesylate is one drug that may be used to treat ADHD in people with ASD.

Alpha-2 adrenergic receptor agonists

Guanfacine and clonidine are examples of alpha-2 adrenergic agonists that have shown promise in the treatment of ADHD in ASD. In a double-blind placebo crossover study, transdermal clonidine was effective in reducing the symptoms of autism in nine male autistic individuals, ages 5 to 33. More recently, in a multisite randomized placebo-controlled trial including 62 children with ASD (mean age of 8.5 years), extended-release guanfacine was found to be safe, well-tolerated, and effective in lowering hyperactivity, distractibility, and impulsivity.

Treatment for anxiety and depression

Comorbidity rates for anxiety disorders are high among children and adolescents with ASD; they vary from 40 to 84% for any anxiety disorder, 8 to 63% for specific phobias, 5 to 23% for generalized anxiety, 13 to 29% for social anxiety, and 8 to 27% for separation anxiety. When treating anxiety in individuals with ASD, selective serotonin reuptake inhibitors (SSRIs) such citalopram, sertraline, fluoxetine, and fluvoxamine are commonly utilized. Though it hasn't been well studied in ASD, sertraline combined with cognitive-behavioral therapy has been demonstrated to be beneficial in treating juvenile anxiety. All of these SSRIs have demonstrated potential in treating anxiety problems in children.

Another drug that has shown some potential in treating anxiety in children with ASD is buspirone. More research is needed to thoroughly evaluate propranolol's potential for treating anxiety in children with ASD, despite the fact that this classic beta-adrenergic antagonist has lately shown positive cognitive effects in the brains of individuals with ASD. Research on the effectiveness of SSRIs in treating depression in children with ASD is lacking. However, fluoxetine can be required if a child with ASD is suffering from severe depression. In general, therapeutic decisions regarding the treatment of depression in children and adolescents with ASD should be made on an individual basis.

Treatment for sleep disorders

At about 40–80% of kids with ASD have sleep issues, compared to 25–40% of kids with typical development. Common issues include excessive daytime tiredness, aversion to bed, and insomnia. A meta-analysis found that melatonin is well recognized and may improve sleep and daytime patterns. A Phase III trial found that melatonin accelerated sleep in 146 children with neurodevelopmental problems, but it had no appreciable impact on behavior or family relations. Since low melatonin levels can disrupt the circadian cycle in children with autism, melatonin is often recommended when other therapies fail. Prolonged-release melatonin may be more effective for those who are intolerant to conventional formulations. Since melatonin is not FDA-regulated, caregivers should seek formulations that have it as the only active ingredient.

Bipolar disease and mood lability treatment

Anti-epileptic drugs are used to treat bipolar disorder and mood instability in children with ASD, as well as impulsivity, irritability, aggression, and hostility. A randomized, double-blind, placebo-controlled study evaluated the efficacy of divalproex sodium in treating irritability in 55 children with ASD, using the ABC and CGI-I Irritability subscales as the primary outcome measures. Both irritation and aggression exhibited statistically significant reductions, according to the results. Additional evidence suggests that aripiprazole and risperidone may be useful in treating mood instability.

Treatment of social disability, repetitive behaviors and self-injurious behavior

Disability in society

You can find a summary of the treatment of social difficulties elsewhere. One instrument for evaluating social impairment in kids with ASD is the ABC's parent-rated Social Withdrawal subscale. This subscale measures social impairment by documenting identifiable behaviors in response to interactions that are initiated by others and the degree to which the child initiates the engagement. A secondary analysis of ABC Social Withdrawal subscale data from two multicenter studies revealed that risperidone was effective in addressing social impairment in children with ASD after 8 weeks of treatment.

Repetitive behaviors and circumscribed interests

A Cochrane review that looked at nine randomized controlled trials with 320 participants found no evidence that SSRIs (fluoxetine, fluvoxamine, fenfluramine, or citalopram) were helpful in treating repetitive behaviors and limited interests in children and adolescents with ASD, despite some studies suggesting that they might. This is because SSRIs frequently cause behavioral activation when used in ASD.

Self-injurious behavior

One of the most difficult behavioral abnormalities in ASD is self-harming behavior, which is especially upsetting for parents. Hand biting, slamming the head into hands or objects, and skin scratching are a few examples of this type of behavior. Risperidone has been shown to be useful in treating self-harming behavior, particularly in extreme circumstances. Based on the idea that people with ASD who engage in self-harming behaviors have dysfunctional pain management, opioid antagonists like naltrexone have been used to treat these behaviors. While open-label research indicates that naltrexone may help children with autism and self-harming behavior.

Disorder-modifying treatments

The relevant observations are outlined in this section. A paradigm change in the understanding of the pathophysiology of ASD in recent years has made it possible to identify new candidates that may serve as agents that modify the disorder.

Sulforaphane

Cruciferous vegetables include sulforaphane, a substance that increases the expression of antioxidant genes involved in regulation mechanisms via the Keap1-Nrf2 cytoprotective signaling pathway. This results in changes to neuroinflammation, antioxidant capacity, and oxidative stress. In a recent randomized double-blind placebo-controlled experiment, sulforaphane was assessed in 44 young males with moderate to severe ASD, ages 13 to 27 (29 on active therapy and 15 on placebo). According to changes in the ABC Irritability subscale, Social Responsiveness Scale (SRS), and CGI-I scores, patients who received daily doses of 50–150μmol sulforaphane for 18 weeks showed statistically significant improvements in their verbal communication, irritability, hyperactivity, and social interaction scores when compared to those who received a placebo. The effectiveness of sulforaphane will need to be confirmed by additional assessment in larger-scale clinical trials.

Oxytocin

To find out if intranasal oxytocin (24 international units (IU)) could improve eye gaze behavior, a crucial indicator of social communication difficulties in ASD, 32 adult males with ASD and 32 placebo controls were tested using Tobii eye tracking in a randomized double-blind placebo-controlled trial. The visits were spaced one week apart. This study demonstrated that intranasal oxytocin enhanced eye gazing behavior in both the autism and placebo groups. The intranasal oxytocin treatment was more beneficial for patients in the autism group who looked at their eyes less frequently.

N-acetylcysteine

As a prodrug of L-cysteine, N-acetylcysteine is quickly absorbed when taken orally. Consequently, glutamate is shuttled out of the cell as a result of cystine absorption, making it essential for controlling extracellular glutamate levels. This is significant since disruption of glutamatergic neurotransmission and glutathione production have been identified as potential causes of ASD. N-acetylcysteine has been shown to be effective in alleviating irritability in children with autism, according to a randomised placebo-controlled trial. N-acetylcysteine is a useful supplement to risperidone for the treatment of irritability in children aged 4 to 12 years, according to a recent randomized double-blind placebo-controlled study.

d-cycloserine

D-cycloserine, which was first recognized for its efficaciousness as an antibiotic in the treatment of pulmonary tuberculosis, has drawn interest due to its possible application in the management of mental illnesses. According to a pilot study, using d-cycloserine, a glycine partial agonist at the N-methyl-d-aspartate (NMDA) receptor, significantly reduced social disengagement in autistic people. Others have more recently noted that d-cycloserine helps those with ASD aged 14 to 25 with their social deficits and stereotypies.[2]

Dietary Supplements

Sulforaphane is a naturally occurring isothiocyanate (found in broccoli and other cruciferous vegetables) Sulforaphane is an antioxidant, anti-inflammatory, and mitochondrial protective agent that has been studied in several animal models and humans with neurodegenerative and neurodevelopmental disorders]. Sulforaphane is a sulfur-rich dietary phytochemical which can penetrate the blood brain barrier, and it subsequently induces the nuclear factor erythroid 2 related factor 2 (*Nrf2*) signaling cascade that stimulates the expression of more than 200 genes that are antioxidants and involved in detoxification and neuroprotection in the CNS [The effect leads to reduction of superoxide and other reactive oxygen species (ROS), upregulation of the proteozome system to digest unfolded or misfolded proteins, enhancement of autophagy, inhibition of pro-inflammatory cytokines, protection from heme toxicity, and defense of neuronal cells from $A\beta_{42}$-mediated cytotoxicity.By promoting the conversion of oxidized glutathione into reduced glutathione, other antioxidants, such as omega-3 fatty acids, have been investigated in ASD with varying degrees of success.[6]

CONCLUSION

A complex and multidimensional neurodevelopmental disease, autism spectrum disorder (ASD) affects behavior, social interactions, and communication. Each person experiences it differently; symptoms can range from moderate to severe, and medical comorbidities like depression, anxiety, and ADHD are frequently present. Both genetic and environmental variables are thought to have a role in the emergence of ASD, while the precise causes are yet unknown. Since there are presently no approved medications to treat the primary symptoms of ASD, behavioral therapies are usually used in conjunction with other approaches to effectively manage the disorder. On the other hand, certain comorbidities and symptoms, like anxiety, hyperactivity, and irritability, are treated with drugs Better diagnostic instruments and treatment alternatives are anticipated to be discovered as research progresses, emphasizing the value of tailored care and enhancing the quality of life for people with ASD. More research into the neurodevelopmental pathways, genetic variables, and biological processes that underlie ASD is probably going to lead to more targeted treatments and improved long-term results for individuals impacted.

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