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Review article

Understanding autism spectrum disorder and its treatment options

Noor Ahmed Giasuddin[1], Rokeya Tasnin[2], Mohammad Muntasir Maruf[3]

Summary

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with impairments in social communication and interaction, restricted interests, and repetitive behaviors. According to a recent study, ASD occurs in approximately sixteen out of every 1,000 children. Children with ASD often suffer from mental retardation, seizure disorder, and psychiatric disorders such as depression and anxiety. Early detection and intervention of this condition can significantly improve outcome, with about one third of persons with ASD achieving some degree of independent living. Current research links autism spectrum disorder to biological or neurological differences in the brain. Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) scans show abnormalities in the structure of the brain, with significant differences within the cerebellum, including the size and number of Purkinje cells. In some families there appears to be a pattern of autism or related disabilities, which suggests there may be a genetic basis to the disorder, although at this time no one gene has been directly linked to autism. There are three large categories of treatment for this disorder: behavioral modification and communication approaches, dietary and nutritional approaches, and complementary approaches. This review paper discusses all of these broad categories and the sub-categories associated with them.

*1. Assistant Professor, Department of Psychiatry, Faridpur Medical College, Faridpur, Bangladesh. Cell: +8801713682456.
E-mail: sadidhk@gmail.com
2. Staff Psychiatrist, Access Counselling Services, Ohio, USA.
3. Assistant Professor, Department of Psychiatry, Shaheed M Monsur Ali Medical Collage, Sirajganj, Bangladesh.

*Corresponding author

Introduction

Autism spectrum disorder is a complex neurodevelopmental disorder with core features of difficulty with social communication and interaction, restricted interests, and repetitive behaviors. A number of other associated symptoms frequently coexist with autism. According to recent study in USA, 1 in 59 individuals is diagnosed with autism, making it more common than pediatric cancer, diabetes, and AIDS combined. It is four times more likely to strike boys than girls. In families with one child with autism, the risk of having another child with autism is 3-8%. Pairwise autism spectrum disorder concordance was 31% for dizygotic and 88% for monozygotic twins.[1]

Materials and methods

Literature search was performed with the key words "Autism", "Autism Spectrum Disorder", "Treatment of Autism", "Brain changes in Autism". Representative and leading researches from last 15 years were included in the study.

Results and discussion

We have summarized the findings under different representative headings and sub headings.

Autistic brain overview

Autism research indicates that autism may be a disorder of the cortex area of the brain which controls reasoning, problem-solving, memory, voluntary movement and sensation.[2] Research results include the following findings:

Brain growth: The brain of some children with autism grows larger and develops faster than children experiencing normal brain development at around 12 months. The expansion occurs primarily in regions that process visual information. Brain volume overgrowth is linked to the emergence and severity of autistic social deficits.[3,4] Brain structure: The sizes of certain areas of the brain, such as the corpus callosum and amygdala, are different in people with autism than in unaffected people. The corpus callosum has smaller middle and back lobes and the amygdala is larger than the same brain areas in people with typical brain development. People with autism may have multiple brain structure differences.[3,4] Brain function: The autistic brain functions differently than an average brain. The structural differences in the brain, such as minicolumns (a vertical column through the cortical layers of the brain; neurons within the microcolumn receive common inputs, have common outputs, are interconnected, and may well constitute a fundamental computational unit of the cerebral cortex), may cause a person with autism to think, perceive and react to things differently than a person with typical brain development.[5]

Causes

Currently autism is viewed as a multifactorial disorder. It is thought that neurologic abnormality causes the disorder, but the exact cause is unknown in most cases. Researchers suspect that a number of different genes that, when combined together, increase the risk of getting autism. Environmental factors in prenatal, neonatal and postnatal periods like gestational diabetes, neonatal hypoxia, exposure to air pollution, parental immigration or sensory/social deficits, all seem to play roles in causation.[6] In some children, autism is linked to an underlying medical condition. Examples include metabolic disorders like untreated phenylketonuria;[7] congenital infections like rubella, cytomegalovirus, and toxoplasmosis;[8] genetic disorders like fragile X syndrome, and tuberous sclerosis;[9] developmental brain abnormalities like microcephaly, macrocephaly, and cerebral dysgenesis;[10] and neurologic disorders acquired after birth like lead encephalopathy or bacterial meningitis. These medical disorders alone do not cause autism as most children with these conditions do not have autism. Environmental factors and exposures may interact with genetic factors to cause an increased risk of autism.[11]

Diagnosis

Parents' Observations: Parents are often the first to notice that something is not right with their child, such as – unresponsive from birth, cry excessively, not make eye contact, focus obsessively on an object for a long period of time, become indifferent to others, lose imaginative play skills, do not respond to their name, and become uninterested in playing with other children.

Initial evaluation: Initial evaluation includes observational data and a developmental screening. In addition, several tools are commonly used to screen for autism, including the Checklist of Autism in Toddlers (CHAT) and the Comprehensive Autism Ratings Scale (CARS). CHAT assesses using a scoring mechanism of key items that splits results into three risk groups. CARS was designed to help differentiate children with autism from those with other developmental delays, such as intellectual disability.

Because there is no medical test or biomarker for autism, diagnosis is based on observation of the child's behavior, educational and psychological testing, and parent reporting. A team of specialists is usually involved in the diagnosis. The team may include a neurologist, psychiatrist, developmental pediatrician, psychologist, gastroenterologist, audiologist, speech therapist, occupational therapist, and other professionals. Usually the team members evaluate the child, assessing his or her strengths and weaknesses, and then explain the test results to parents.

Treatment

There is no standard treatment for autism, and different professionals have different philosophies and practices in caring for their patients. A common strategy includes a specialist, who will present each type of treatment, give the pros and cons, and make recommendations based on published treatment guidelines and his or her own experience. The decision of which treatment to pursue is made with this specialist (with input from other members of the care team) and family members, but the decision is ultimately of the parents. The specialist should help parents to understand exactly what will be done and why, and what can be expected from the choices.

There is no cure for autism, nor is there a standard therapy that works for all people with autism. Different approaches work for different people. Accepted interventions may work for some and not for others. Most people with autism show developmental progress and respond to a combination of treatment and education. There is some evidence that the earlier behavioral, educational, speech, and occupational therapy is begun, the better is the long-term outcome.[12] Treatment strategies used in autism include behavioral, educational, biomedical, and complementary therapies. It is important to consider evidence-based interventions as much possible.

Applied Behavior Analysis (ABA)

ABA is a well-developed scientific tool that focuses on the analysis, design, implementation, and evaluation of social and other environmental modifications to produce meaningful changes in a person's behavior. ABA is based on the fact that an individual's behavior is determined by past and current environmental events in association with their genetic endowment and physiological variables. ABA uses observation, measurement, and functional analysis of the relationship between environment and behavior and uses changes in environmental events, such as antecedent stimuli and consequences, to produce practical and significant changes in behavior. In case of autism, ABA focuses on treating the problems of the disorder by altering the individual's social and learning environments.[13]

Comprehensive ABA attempts to treat multiple developmental domains, such as cognitive, communicative, social, emotional, and adaptive functioning. Early intensive behavioral intervention is the preferred target to close the gap between the person's level of functioning and that of typically developing peers. These programs tend to range from 30-40 hours of treatment per week. Initially, treatment is typically provided in structured therapy sessions, as the client progresses treatment in different settings and in larger community is provided. Training family members and other caregivers to manage problem behavior and to interact with the individual with ASD in a therapeutic manner is a critical component of this treatment model.[13]

ABA Approach: Discrete Trial Training

It is a structured ABA technique that breaks down skills into small, "discrete" components. It consists of a series of distinct repeated lessons or trials taught one-to-one. This technique is usually implemented when the person is young, before the age of six. Each trial consists of a prior, a "directive" or request for the individual to perform an action; a behavior, or "response" from the person; and a consequence, a "reaction" from the therapist based upon the response of the person. Parent training is a necessary part of an effective program. The person's progress is closely monitored by the collection of data on the performance of each trial. After a skill has been mastered, another skill is introduced, and the mastered skill is placed on a maintenance schedule.[14]

ABA Approach: Pivotal Response Therapy

Pivotal response therapy (PRT) is a behavioral intervention therapy for autism. Pivotal response therapy is based on the belief that behavior connects primarily on two 'pivotal' behavioral skills, motivation and the ability to respond to multiple cues, and that development of these skills will result in overall behavioral improvements. Play environments are used to teach pivotal skills, such as turn-taking, communication, and language. Pivotal response training involves specific strategies such as clear instructions and questions presented by the therapist, child choice of stimuli (based on choices offered by the therapist), intervals of maintenance tasks (previously mastered tasks), direct reinforcement (the chosen stimuli is the reinforcer), reinforcement of reason for purposeful attempts at correct respond, and turn taking to allow modeling and appropriate pace of interaction.[15]

ABA: Reciprocal Imitation Training

Reciprocal imitation training was developed to teach spontaneous imitation skills to young children with autism in a play environment. This procedure includes unexpected simulation in which the therapist imitates actions and vocalizations of the child. It can increase children's social behaviors such as coordinated attention after reciprocal imitation training, suggesting that both the imitative and the spontaneous play could be taken on a social quality.[16]

ABA: Self-management Technique

Self-management has been developed as an additional option for teaching school-age children with autism to increase independence and generalization without increased reliance on a teacher or parent. Self-management typically involves some or all of the following components: self-evaluation of performance, self-monitoring, and self-delivery of reinforcement. Ideally, it includes teaching the child to monitor his/her own behavior in the absence of an adult. Study shows that the preschool-age students using self-management training learned new activities using favorite toys that typically required assisted play. Children were prompted to engage in new behaviors with the toys, and were asked to take a token whenever they displayed a variation in the target behavior.[17]

ABA: Video modeling

Video modeling uses predictable and repeated presentations of target behaviors; however, these behaviors are presented in video format, thus reducing variations in model performance. Video modeling has been shown to improve various skills in individuals with autism, including conversational speech: verbal responding, helping behaviors, and purchasing skills. This medium could increase vocabulary, emotional understanding, attribute acquisition, and daily living skills. Video modeling interventions have used both self-as-model and other-as-model methods. In the first instance, individuals act as their own models, and the video is edited so that only desired behaviors are shown. The second and perhaps more essential method of video modeling employs recording other individuals, typically adults or siblings, performing target behaviors.[18]

Vitamins, minerals, and dietary interventions

Claims regarding the efficacy of vitamins, minerals, or other nutrients in autism are not backed by definite scientific evidence in most cases, but parents and physicians have reported improvement in symptoms in autistic people who were given certain supplements, including vitamin B12, Vitamin D, Omega-3 fatty acid, Folinic acid, Camel milk, Probiotics and digestive enzymes.[19] Some persons with autism have food sensitivities and food allergies and dietary management is important to in these cases to maintain nutrition and health. Another focus of dietary therapy is on problems with intestinal digestion and absorption of nutrients in foods suspected to be present in some individuals with autism. Some parents and professionals have reported improvements in symptoms of autism when diets eliminating suspect proteins, such as gluten (found in wheat flour), are consistently followed. However, there are no studies to confirm their effectiveness.[19]

Medications

Medication does not treat the underlying neurologic problems associated with autism. Rather, medication is given to help manage behavioral manifestations of the disorder, such as hyperactivity, impulsivity, attention difficulties, and anxiety. In most cases, medication is given to lessen these problems so that the person can receive maximum benefit from behavioral and educational approaches. Medications used in autism are psychoactive, meaning they affect the brain. Those used most often include the following:

Antipsychotic drugs: Risperidone, Aripiprazole and some other atypical antipsychotics are successfully used in autism. These drugs have been found to reduce hyperactivity, repetitive behaviors, withdrawal, and aggression in some people with autism.[20]

Antidepressants: Selective serotonin reuptake inhibitors (SSRIs) are prescribed for the treatment of conditions often comorbid with autism such as depression, anxiety and obsessive-compulsive behaviors. But emerging evidence suggests not using these drugs.[21]

Stimulants: Stimulants used to treat attention deficit hyperactivity disorder (ADHD) may help some people with autism. These drugs work by increasing the person's ability to concentrate and pay attention and by reducing impulsivity and hyperactivity.[22]

Anticonvulsant drugs: Anticonvulsants are frequently used to manage seizures in people with autism. Anticonvulsants may also be used to stabilize mood and/or behavior.[23]

Repetitive transcranial magnetic stimulation (rTMS)

Transcranial magnetic stimulation (TMS) is a noninvasive method to excite neurons in the brain: weak electric currents are induced in the tissue by rapidly changing magnetic fields.[7] This way, brain activity can be triggered with minimal discomfort, and the functionality of the circuitry and connectivity of the brain can be modified. The outer part of the brain is called the neocortex. Within the neocortex are groups of cells called minicolumns. These minicolumns are the smallest unit of cells capable of processing information. Ordinarily, minicolumns include relatively large cells, called neurons, which allow communication not only within an individual minicolumn but also among different parts of the brain. Minicolumns in people with autism are smaller and more numerous than normal. In addition, neurons within each minicolumn are reduced in size.

This may impair brain activities that require longer projections (e.g., language), whereas reinforce those that depend on shorter connections (e.g., mathematical manipulations). According to Casanova et al., the extra minicolumns with extra-small cells may explain the hypersensitivity of some autistic patients as well as their seizures. It is possible to increase the "insulation" surrounding minicolumns, thus lessening sensory overload and the likelihood of seizures.[24] According to Casanova et al., the "main property of these minicolumn cells and projections is that they stand at 90 degrees to surface of the cortex. They are the only cells that do so. Transcranial magnetic stimulation (TMS) could flip the magnetic field in the cortex, thus reinforcing the insulation around the minicolumns.[24]

Stem cell therapy

Children with autism suffer from two major conditions: Hypoperfusion and Immune Dysregulation.25 Hypoperfusion of the brain in autism: Children with autism have shown impaired blood flow (hypoperfusion) to the brain. Hypoperfusion may contribute to functional defects not only by inducing hypoxia (an oxygen deficit that prevents normal brain function) but also by allowing for abnormal metabolite or neurotransmitter accumulation. The areas affected by hypoperfusion seem to correlate with regions of the brain that are responsible for functionalities that are abnormal in autism. Hypothetically, if perfusion can be improved through the revitalization of blood vessels (angiogenesis), then this should also allow for metabolite clearance and restoration of functionality.[25]

Immune dysregulation in autism

Successful neurodevelopment is contingent upon a normal balanced immune response. Children with autism have immune systems that do not function normally; instead an autoimmune response of the nervous system appears to prevail. Astrocytes (supportive brain cells) that normally play a critical role in regulating perfusion and protection against central nervous system infection, have the potential to cause damage to the host when functioning in an aberrant (i.e. auto-immune) manner. Autistic children often have continually suppressed immune systems and chronic inflammation. Immune dysregulation is also very apparent in gastrointestinal health.[25]

Rationale for using Stem Cells to treat autism

The administration of CD34+ umbilical cord cells and mesenchymal cells were proposed as novel treatments for the two pathologies associated with autism – hypoperfusion to the brain and immune dysregulation. Using these two kinds of stem cells together may potentially heal both the brain and the gut. Treatment of hypoperfusion defect with umbilical cord blood CD34+ stem cells. Angiogenesis - the formation of collateral blood vessels - is believed to be fundamental in neurological recovery. A promising method of increasing angiogenesis into damaged areas is by administration of CD34+ stem cells.[25] Umbilical cord blood has highly active CD34+ cells that, following injection into a patient, should induce angiogenesis in areas of cerebral hypoperfusion. Consequently, improved blood flow and oxygen to the brain should also improve nervous system functioning.

Immune modulation by mesenchymal stem cells

The treatment of immune dysregulation in autism is expected to profoundly influence neurological function. The ability of mesenchymal stem cells to suppress pathological immune responses (e.g. inflammation) and to stimulate hematopoiesis (blood cell regeneration) leads to the possibility that these cells may also be useful for treatment of the defect in T cell numbers associated with autism. The review by Ichim et al. suggests that allogeneic mesenchymal stem cells administered to suppress inflammation may be used without fear of immune-mediated rejection.[25]

Conclusion

As of the information known by today, there is no cure for autism, nor is there a standard therapy that works for all people with autism. Different approaches work for different people. Accepted interventions may work for some and not for others. Different professionals, each with excellent credentials and experience, may disagree about what is the best approach for the child. An individualized treatment plan designed to meet his or her unique needs is essential.

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