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Autism spectrum disorder: Current progress in therapeutic options for mitochondrial dysfunction and ongoing management possibilities with a multifariousness: A critical overview

Sushil Giri [1,*], Subhranshu Panda [1] and Raghav Mishra [2]

[1] *Department of Pharmacology, MIT College of Pharmacy, MIT Group of Institutions, Moradabad-244001, Uttar Pradesh, India.*
[2] *Institute of Pharmaceutical Research, GLA University, Mathura-281406, Uttar Pradesh, India.*

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in interactions, social skills and communications. It consists of an inability to acquire social and emotional skills during early developmental age that to one to two years of the age which progressively results in variable degrees of social adaptation incapacity. Over the last 20 years, the frequency of ASD has progressively increased, with a recent estimate about 1 in 36 children and with boys 4 times more susceptible to the development of ASD than girls. The etiology of ASD is multifactorial and includes functional and structural neurological abnormalities. There is an alarming lack of knowledge in the subject among health care professionals. Hence it is needed to be aware of the people and manages aggressive behavior, hyperactivity, and irritability. Past two decades many efforts have focused on the determination of genes associated with autism, immune dysfunction and free radicles contributing to ASD. The present article aims to highlight the current state knowledge regarding the role of mitochondrial DNA (mtDNA) in the etiology of ASD, core symptoms, diagnosis, therapeutic aspects (meditational and non-meditational) and the prediction of clinical outcomes in the future.

Keywords: Autism spectrum disorder; Diagnosis; Free radicles; Gene; Mitochondrial DNA; Diagnosis

1. Introduction

Autism spectrum disorder (ASD) is a multifaceted neurobehavioral developing disorder that has evolved into a critical condition affecting neurodevelopment [1]. The term ASD refers to a collection of illnesses that include Autism disorder, Pervasive developmental disorder, Asperger disorder and the Diagnostic and Statistical Manual of Mental Disorder [2]. Now, all of these disorders are grouped as ASD. It usually manifests itself in the first two or three years of life and affects one's capacity to speak and socialize with others [3]. It is also frequently associated with significant behavioral difficulties, repetitive patterns of behavior (hand flapping, rocking and spinning), difficulties in pronunciation, facial expressions, aggressiveness, self-destructive acts, influences communication skills, developing relationships, and significant challenges which are atypical patterns of behavior. It is commonly seen in children and autism may fight with social interactions because they are incompetent to relate to their peers [4, 5].

In 1943, Leo Kanner described ASD for the first time [6]. The incidence of ASD and the associated symptoms differ from person to person and might vary in severity from modest to severe, and can evolve over time [7]. Pharmacological therapies are frequently beneficial and necessary for raising the standard of living and function; early diagnosis and treatment are important to improve functionality and standard of living as well [8]. However, there is no medical test

* Corresponding author: Sushil Giri

for the identification of autism. It can diagnose based on observing the activities of the child, how is the child responding, talks, and acts in comparison to the other children of the same age group. Autism is a lifelong heterogonous condition and it is four times more common in boys as compared to girls. However, many children who are diagnosed with ASD, live independently, productively and successfully [9]. Despite enormous research endeavors, the exact pathophysiology behind ASD remains largely unknown, but is believed to involve a complex interplay between genetics and environmental factors, autism history, prenatal and perinatal factors, mtDNA mutation, neuro-anatomical deformities, anxiety, depression, sleeping condition and gastrointestinal disease [10].

Manivasagam T, *et al*., discussed increased oxidative stress and a reduction in antioxidant capability have been related to ASD and measured glutathione and antioxidant levels that were found engaged in the defense system against reactive oxygen species (ROS) [11]. Several investigations have been suggested changes in the antioxidant enzyme (superoxide dismutase, glutathione peroxidase) [12]. Autism has also shown changed levels of glutathione and homocysteine increasing inflammation and mitochondrial dysfunction [13]. A patient with ASD typically can be diagnosed during early childhood, 2-3 years of age by using behavioral observation and clinical interviews. ASD symptoms generally appear in early childhood with indications of delayed growth before the actual age of three [14]. The American Academy of Pediatrics recommends at least 12 months of autism screening for early identification [15].

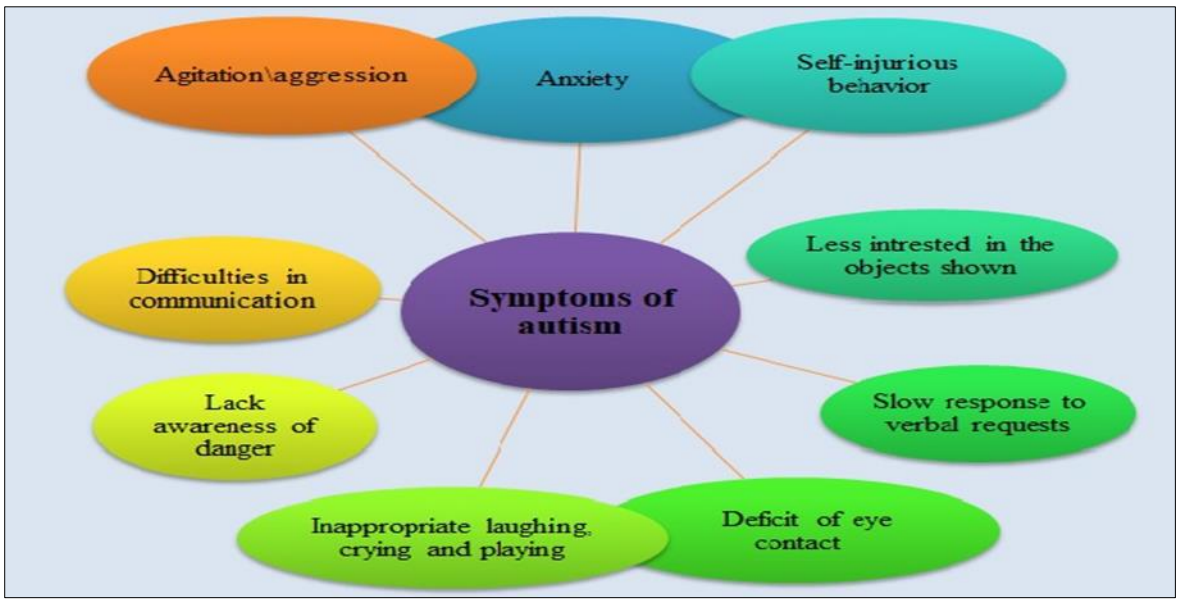

Figure 1 Symptoms of Autism

2. General diagnosis

2.1. Diagnosis in Toddlers

ASD can be diagnosed by a variety of experts (psychologists, pediatricians and psychiatrists), with the best results coming from a multidisciplinary approach [16]. Two standardized diagnostic tools are available: the STST (Screening Tool for Autism in Toddlers) and the ADOS (Autism Diagnostic Observation Schedule). These tools allow the clinician to watch and define the specific activities of the individuals suspected of having ASD while accompanied by the care-giver [17]. The Autism Diagnostic Interview-Revised (ADI-R) and the Diagnostic Instrumental for Social Communication Disorders, are two caregiver assessment. It is used by many clinicians to measures child's symptoms by the Childhood Autism Rating Scale (CARS) and Social Responsiveness Scale (SRS) [18].

2.2. Diagnosis in Minors and Adolescents

The Minors and Adolescents who have a family history of mental health issues are concerned and the diagnosis are different for them [19]. Individuals with autism are commonly diagnosed with co-occurring problems such as anxiety, hyperactivity, or mood disorders which may have later exacerbated or marked the ASD [20, 21]. These children's assessments involve the same ASD-specific clinician observations and caregivers report information on speech, language, verbal and nonverbal cognitive and adaptive abilities as well as consideration of any relevant mental illnesses [22]. High-risk infants by the 12 months of age reveal reduced vocalization, orienting to name and gaging to face.

Furthermore, by 18 months of age, it appears to be a reduction in social smiling, social commitment, contraction to their mother during naturalistic interactions, and nonverbal skills [23]. Loh and other researchers analyzed ASD from high and low-risk samples from repetitive movements in children during a semi-structured evaluation and noticed the prevalence of arm waving in one and two-year-old siblings [24]. Libertus *et al*., and other researchers used the Mullen Scale of Early Learning (MSEL) to assess toy play at six months and discovered that high risk neonates exhibit less developed object manipulation and fewer seizing action than infants without a family background of ASD. Futhermore, suggested that impaired motor maturity delayed independent sitting and reduced postural stability, rhythmic arm motions during the first year of the age in high-risk infants using the Alberta Infant Motor Scales(AIMS) [25, 26]. Leo Kanner *et al*., released a report on "Autistic disturbance of affective contact" which included eight boys and girls in a case study from 2 to 11 year olds, Kanner noticed to having an immense inability to relate to others that appeared to be present throughout childhood and also found abnormal language development, repetitive behavior and a tendency to illuminate things literally [27].

3. Prodromal Symptoms

Zwaigenbaum *et al*., and other researchers have found the obstruction in early sensory, motor function, and irregular emotional activities are substratum of ASD. It manifests more directly with ASD diagnostic criteria in the very first year of life before the advent of social communication. They also compare nondiagnosed high risk children to control at 12 to 18 months and found that nondiagnosed individual has lower gross motor scores on MSEL [28, 29]. Ozonoff *et al*., compared those high-risk infants with no family history of ASD at 9 to12 months of age later high-risk infants were reported developmental disability and showed obstruction in such as unusual visual exploration spinning, rotating and also examined atypical sensory oriented behavior such as intensive visual inspection [30].

4. Mitochondrial and Genetic Abnormalities in ASD

Mitochondria are the small, double membrane-bound cellular organelles that keep the cell full of energy and for the neurodevelopment and function, manage energy generation [31,32]. Mitochondrial anomalies in ASD children in there early years have become a matter of agitation. Young children are frequently being investigated by many researchers who are suffering from mitochondrial abnormalities [33]. Mitochondrial disturbances defects in biochemical reactions within the mitochondria and mutations of mtDNA (mitochondrial DNA mutation) disrupt the mitochondria's biochemical reaction. Long-time mitochondrial malfunctioning may lead to serious health issues [34]. Mitochondrial malfunctioning can be controlled with better lifespan and quality of life if caught early. With a substantial number of children with autism who have metabolism such as high lactate lavels and other biochemical abnormalities, early detection of mitochondrial illness is critical [35, 36]. A tiny proportation of people with ASD have very little DNA modifications but only approximately 20 percent are discovered in a certain gene problem like fragile X syndrome [37]. The remaining with ASD have chromosomal aberration other genetic or hereditary reasons and error in the epigenetic process (15q11-q13 duplication syndromes) [38]. Genetic and molecular anomalies in ASD will be better characterized using next-generation DNA sequencing methods including mitochondrial genome abnormalities, espically in smaller children [39, 40]. Sebat *et al*., discussed the etiology of ASD, it is the most complex with a strong genetic influence that encompasses the roles of genes**.** For a teenage patient with developmental delay and behavioral issues, many types of genetic and biochemical tests are now accessible [41, 42].

According to Alzghoul *et al*., vitamin D has been connected to the treatment of the early developmental etiology of ASD by influencing the expanding immune system [43]. Mahesh *et al*., investigated the role of mRNAs in controlling the interplay of genetic and environmental factors. Furthermore recognized the role played by circadian variables, including immunological inflammation, sleep disorders and decreased circadian neuroendocrine responses on the pathogenesis of ASD [44]. *Zingiber officinale*, *Astragalusmembranaceu*, *Ginkgo biloba*, *Centellaasiatica* and *Acoruscalamus* are some of the herbal remedies recommended by Kardani *et al*., with a neuroprotective impact on those with ASD [45]. Rossignol DA *et al*. suggested Melatonin Physiology Anomalies (MPA) in ASD individuals. Abnormalities in melatonin may be genetic mutations in the melatonin pathways [46]. Recent melatonin-supplemented meta-analysis of five randomized, double-blind studies in ASD showed significant benefits in sleep duration, reduced night time arousal and better sleep [47]. Pacheva and Ivanov *et al*., discussed glutathione decreases the mitochondrial protection against oxidants and tumor necrosis factor (TNF)-α; immune dysregulation and inflammation inhibit mitochondrial function through TNF-α; autoantibodies against folate receptors underprin cerebral folate deficiency, resulting in disturbed methylation, and mitochondrial dysfunction. Furthermore discussed biological-based therapy for ASD management by folic acid supplementation has a favorable impact in ASD symptomatic patients with folate receptor autoantibodies [48, 49].

5. Management and prevention of ASD

When a teenager is diagnosed with ASD, relevant encouragement and counselling should be made available to the family toward therapy and service possibilities [50]. There are a variety of resources available, including the National Institute of Health (NIH) and a number of commercial organization those provide home based services, such as Autism Society of America, Autism Speaks, and the America Academy of Pediatrics. [51]. It should include precise evidence of the diagnostic examination for ASD behavioral and educational treatments. Many states currently have legislation requiring private insurance to cover behavioral treatments for ASD [52]. The early intervention team should assess children with ASD and an individualized family service plan (IFSP) should be designed for them Older children with age of three should be enrolled in their nearby public school for review to ascertain whether they are eligible for special education [53]. The Centers for Medicare and Medicaid Services (CMS) have ordered ASD services to be covered by public insurance furthermore, autism children should be educated approxamility 25 hours of total service time, according to the National Research Council (NRC) [54].

5.1. Behavioral Therapy

There has been so much study showing early-intensive arbitration may aid youngsters in combating and gaining abilities and enhancing long term results from autism [55]. Recently the gold-standard therapy of ASD was examined using Applied Behavioral Analysis (ABA). ABA's core concept is founded on learning theory, teaching skills. ABA can be applied in developing abilities in communication, socialization, adaptive behavior and cognition [56, 57]. There are many kinds of behavioral therapy accessible, such as the Early Start Denver Model (ESDM) and the Pivotal Response Treatment (PRT) [58]. Targeting basic autistic deficiencies of social engagement, emotional reasoning and social abilities is also done through pragmatic behavioural and play-based treatments [59].

5.2. Allied Services and Therapies

Patients with autism may improve speech, language, and communication via allied services and therapies (Speech and language therapy), gestures and signs (American Sign Language), picture exchange communication systems (PECS), communication boards, visual supports, and devices may be used to support functional communication[60, 61]. Recently occupation intervention is in full swing to inscribe adaptive skill needs, sensory needs as well. Most approaches and instruments such as sensory integration techniques, the use of brushing, and sensory toys can be useful and to get better outcomes [62].

5.3. Counseling

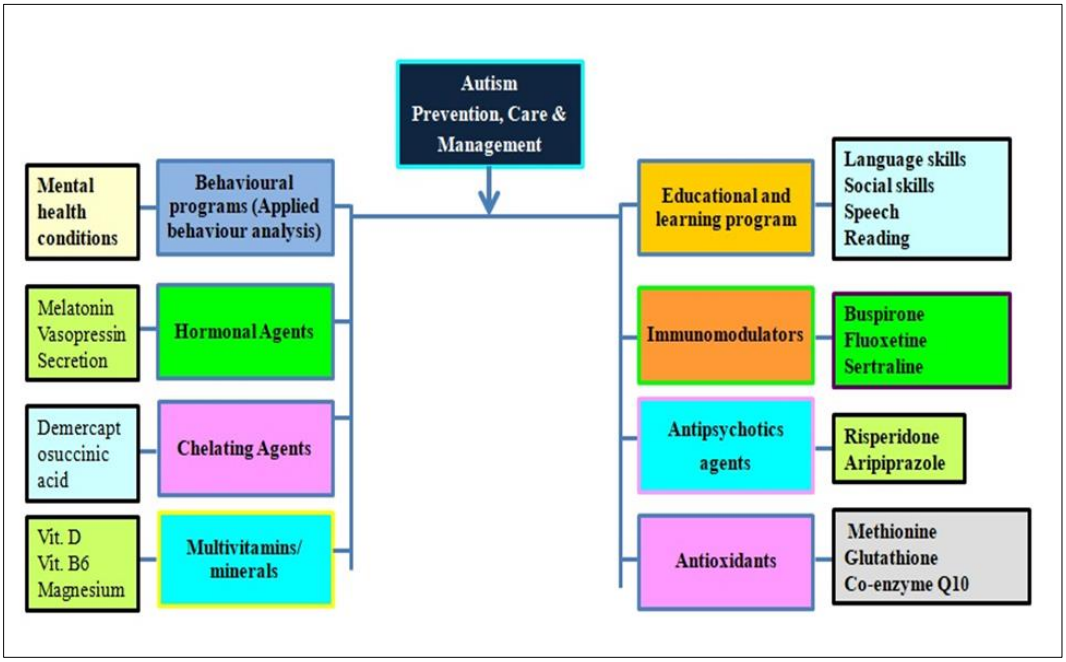

Figure 2 Prevention, Care and Management of Autism

A professional connection may be established through counseling methods to enhance language skills, social skills, communication, repetitive patterns of behavior speech, and nonverbal communication [63, 64]. Cognitive-behavioral treatment approaches (CBT) have been developed for use with the ASD population, which have a positive result, for core symptoms of stiffness and rigidity as well as for the use of comorbid psychiatric conditions [65].

5.4. Pharmacological Therapies

There is no authorized drugs by the Food and Drug Administration (FDA) to manage the fundamental symptoms of autism spectrum condition, therefore there are ongoing research prospects [66]. Drugs that are used to treat mental problems can also help people with ASD. The FDA has just approved two medications, risperidone and aripiprazole for use in this population; both are atypical antipsychotic designed specifically for the treatment of agitation and wrath in children with ASD. Other medicines that have been employed to treat anxiety, hyperactivity, sleep disruption,and include selective serotonin reuptake inhibitors (Fluvoxamine), alpha agonists (Guanfacine) and melatonin. [67, 68].

Aripiprazole's efficacy and safety in children with ASD were studied in double blind randomized controlled trial (RCT) [69]. 218 autistic children and adolescents were administered one of the three different dosages of aripiprazole (5, 10 or 15 mg/d) for 8 weeks. At 8th week all three doses effectively diminished irritability when compared to placebo [70]. Another study also suggested that patients with ASD who have aggressive, self-injurious behaviors, received aripiprazole (8.6 mg/d), for 8 weeks. Found aripiprazole significantly reduced aggressiveness and self-injurious activity [71].

Guanfacine, an alpha-2 adrenergic receptor agonist, has been linked to the treatment of aggressive behavior, sleep disturbance and anxiety. It block norepinephrine neurotransmission in the brainstem, resulting in a reduction in sympathetic outflow and peripheral resistance thereby reducing hyper arousal behavoiurs and anxiety. A four week treatment with alpha-2 adrenergic receptor agonist clonidine reduced aggressiveness and improve social interaction in young ASD patients, according to a double blind RCT [72, 73].

Antioxidant supplementation has been linked to a reduction in autistic behaviors and severity due to changed metabolite levels in the interrelated transmethylation and trans sulfuration pathways [74]. James *et al*., reported two open-label trials in children with autism using methylcobalamin and folic acid. In the first smaller experiment (n=8), 800 mg folic acid plus 100 mg betaine given twice daily for three months increased methionine synthesis. Methylcobalamin administration (n=30) at a dose of 64.5 μg/kg, showed significant cognitive behavioral outcomes [75].

Melatonin (N-acetyl-5-methoxytryptamine) has recently been discovered to be a potent free radical scavenger as well as a broad range antioxidant [76]. Melatonin is a low-weight amphiphilic hormone having an indolic structure [77]. Melatonin was first discovered in the pineal gland of bovine in 1958 [78]. The sleep well cycle, bone metabolism, innate immune system and emotional behavior are all influenced by this biomolecule [79].

Coenzyme Q10 (CoQ10) is also known as ubiquinone. It is a powerfull lipid antioxidant that prevents the formation of free radicals and the oxidation of proteins, lipid and DNA [80]. CoQ10 plays a pivotal role in the oxidative phosphorylation, improves energy, augment the immune system as well as diminishes reactive oxygen species (ROS) [81, 82]. CoQ10 is used as adjuvant therapy as a supplement in varied dosage forms such as oral spray, hard cell capsule, soft shell capsule and tablets [83]. The recommended dose of CoQ10 is 30 to 90 mg/day in divided doses, but suggested amount might be as high as 200 mg/day [81].

5.5. Complementary and Alternative Medicine (Cam) Treatments

In lieu of traditional therapies, parents of children with ASDs may choose for CAM such as dietary changes, vitamins and supplements, acupuncture, chiropractic, chelation, hyperbaric oxygen and immunologic agents in place of conventional treatments [92, 93]. CAM therapies are controversial and have little scientific evidence to date [94]. A recent research through internet survey (n=248) found that parents of children with ASD, inquiring about the CAM usage, probable adverse effects, recommended source, expenses, and reasons for ceasing use of CAMs, which concluded that for CAM therapies, the odds ratios of parents-related efficacy showed a modest improvement[95]. Information on how to assess and monitor alternative therapies should be offered to families. Complementary and alternative medicine therapies should not be used in place of established behavioral therapy, since families should be educated [96].

5.6. Nutritional Supplements, Dietary Interventions

Malnutrition is more common in ASD patients due to reduced energy intake, gastrointestional dysfunction, dyspepsia and nutritional malabsorption as a result, nutritional status in ASD patients should always checked to rule any dietary

deficiencies. [97]. Kawicka *at al*., assessed at the dietary and nutritional status of ASD patients, thay found that they were all underweight and that there food was lacking in vitamin D, calcium, potassium, iron and fibers [98]. In a double blind RCT, (n=1028) with ASD were administered omega-3 and vitamine supplementation. Omega-3 supplimentation found effective in the improving several ASD symptoms [99]. However, a recent study evaluated the effects of nutritional supplements found inconclusive evidence for these agents' therapeutic efficacy on ASD-retated symptoms. Nutritional supplementation can be overcome malnutrition-related side effects in ASD patients [100].

Table 1 Effects of Pharmacological and non-pharmacological therapies in the management of ASD symptoms

Sr. No.	Treatments	Outcomes	References
1.	Behavioral Therapy (ages between 12 to 48 months) (ABA, ESDM, PRT)	Intensify communication, socialization, adaptive behavior and cognition. The child encouraged to boost language, social, cognitive skills and focused on building positive relationships.	[55,58]
2.	Allied Services and Therapies: Speech and language therapy, PECS	Assistance in establishing conscious communication, reduce the challenging or undesirable behaviours brought on by frustration, boost opportunities for interaction, learning and improve speech, language, and communication.	[61,62]
3.	Counseling: CBT	Enhance language skills, social skills, and repetitive patterns of behavior, speech, and nonverbal communication. A positive result, for core symptoms of stiffness and rigidity as well as for the use of comorbid psychiatric conditions.	[64,65]
4.	Pharmacologic Therapies: Risperidone, aripiprazole, fluvoxamin, guanfacin, melatonin, methylcobalamin, folicacid, melatonin and coenzyme Q10.	Significantly reduced aggressiveness and self-injurious activity sleep disturbance, bone metabolism, innate immune system, emotional behaviour and anxiety.	[66,71,75]
5.	CAM Treatments: Dietary changes, vitamins and supplements, acupuncture, chiropractic, chelation, hyperbaric oxygen and immunologic agents.	B6 and magnesium supplements to improve symptoms of mental health disorders. Dimethyl glycine and trimethyl glycine are suggested to improve in language and attention. Scalp acupuncture treatment (SAT) is used to treat ASD with symptoms such speech and language problems, behavioural difficulties, anxiety and sleep problems. It is controversial and has little scientific evidence to date. Found effective in the management of ASD symptoms. Nutritional supplementation can be overcome malnutrition-related side effects in ASD patients.	[90,95,96]

6. Future perspective

Autism was recognized as a disability in India under "The Right to Persons with Disabilities Act, 2016". These medical boards progressed steadily to give expertise in India for specific requirements [101]. In India, a multilevel, multi-pronged approach to working within and across system, as well as creation of new ones, are arising to maximize society duty for all people with neurodevelopmental disorders like autism. It also includes providing teachers and school workers with training and assistance, so that students obtain an appropriate education. Finally, there have been changes in governmental, charitable, and non-governmental methods, as well as in the attitude of families, emerging advocates, and self-advocate, but more is needed [102]. In India there are two interventions are ongoing for autism treatment such as Communication DEALL (Developmental Eclectic Approach to Language Learning) and Parent mediated intervention. These projects provide unique Indian perspective to child and family working [103]. The scientific and medical communities are unable to provide a clear cure for adults and children suffering from this disorder [104]. More than 60

contries backed a resolution at the sixty-seventh Word Health Assembly in May 2014 titled "Comprehensive and co-ordinated efforts for the management of ASD" [105].

The use of stem cells to treat autism is appeared to be an exciting therapy option. Several types of stem cells are now being studied to see if they can help people with autism. The following cell types appear to be the most promising: Firstly Umbilical cord blood stem cells- Scientists hypothesize that these cells could be a useful tool for generating new blood vessel growth in autistic brains. Secondly Mesenchymal stem cell-researchers believe that these cells can cure autism-related immunological de-regulation, support intestinal symptoms and cognitive problems. Recent results revealed that hypoperfusion and immunological changes in the brain are key underlying pathogenetic pathways of autism [106]. A study of 32 patients with autism who received autologous bone marrow mononuclear cells (BMMNC) intrathecal transplantation for 26 months, found improved ISAA score (Indian Scale for Assessment of Autism) and decreased severity on the CGI-I (Clinical Global Impression-Improvement Scale) hence, the promising findings of this clinical investigation point to new options for cellular treatment in autism [107]. Using community expenditures for developing and promoting more widely available treatments schemes, which enable the participation of young children and adults may make more sense. There is an obvious, ongoing need for coordination between health-care, education and other services such as support for challenging behaviors and planning for betterment for individuals with autism [108].

7. Conclusion

Autism spectrum disorder is a complex neurodevelopmental disorder, commonly seen in children. It is defined by age inappropriate, impaired social communication and existence of stereotypic behavior. Due to the neurodevelopmental nature of the disorder, it imposes a burden on parents of children with ASD and affecting between 1-2% of the population. People with autism were subjected to stigmatized and discriminated and they are denied access to health care, education and opportunities to engage and participate in there communities. Accessbility, inclusion and support must be complemented by activities at the community and societal levels. All persons, including those with autism have the right to the best possible physical and mental health. The life of patients with ASD is improved today compared with 50 years ago, with the aid of different types of medical and non-meditational interventions such as behavioral therapy, allied and services therapies, counseling, pharmacological therapy, antioxidant therapy, complementary and alternative medicines and nutritional supplements, dietary interventions**.** Adults with ASD are more likely to be able to communicate, read, drive and live in the community after the treatment. Despite medical and non-medical therapy, there is a scarcity of reported humam clinical research. Autism has been under consideration for a long time because of the growing prevalence. Further research is needed to determine the most decisive therapy modality.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interests.

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