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Neurobiological Bases of Autism

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Abstract

Autism is a neuro-developmental disorder, which is associated with impaired social interactions and communication. The biological basis of autism spectrum disorders (ASD) is still not fully understood. ASD has an early onset in life and a complex, heterogeneous, multifactorial etiology. In this review, we try to include the main findings on the genetic influence, neuropathology, neuron structure, and brain networks considered in Autism. Other findings from peripheral samples of subjects with autism and animal models, which show immune, oxidative, mitochondrial dysregulation, are reported. Then, other biomarkers involved and clinical evaluations from very different systems associated with Autism are reported. Finally, it is attempted to integrate the available evidence, which points to an oligogenic, multifactorial etiology that converges in micro-organization of the cortex, with abnormal functioning of the synapses and abnormalities in very general physiological pathways as inflammatory, immune, and redox systems. Although behavioral and educational therapies have been the mainstay of managing ASD, social, pharmacological, and interventional treatments, have also shown some benefit in ASD subjects. The key architecture of ASD development, which could be a target for treatment, is still uncharted territory. Further work is needed to increase the horizons on the understanding of ASD.

Keywords: Autism; Neurobiological basis; Genetic in ASD; Pharmacological and interventional treatments in ASD

Introduction

Autism is considered a neuro-developmental disorder, which is characterized by impaired social interactions, communication, and restricted and repetitive behavior. Its symptoms become apparent before a child is three y old. Autism affects the information processing in the brain by altering how nerve cells and their synapses connect and organize; although this is not well understood [1].

History and background of autism

An Austrian Psychiatrist, Leo Kanner (1934) first used the term 'Autism' when he studied 11 children within his clinic and recognized that they had a similar group of behaviours from childhood like feeling lonely and a Lack of emotional contact, bizarre and elaborate repetitive routines, muteness, and what he described as abnormal speech [2,3].

An Austrian Paediatrician, Hans Asperger (1944) noticed a similar pattern of behaviours in the children such as strong interest in certain subjects, inappropriate social approaches to other people, poor coordination, lack of common sense, and monotone speech, and also no two-way conversation [1,3].

Epidemiology

Based on the evidence reviewed, the prevalence estimates of autism spectrum disorders were 62/10 000.

While the current estimates are variable, the evidence reviewed does not support the differences in PDD prevalence by geographic region or a substantial impact on ethnic/cultural or socioeconomic factors. However, the power to detect the effects is seriously limited in existing data sets, particularly in low-income countries. While it is known that prevalence estimates have increased over time and these vary in different neighboring and distant regions, these findings most likely represent an increase of the diagnostic concepts, diagnostic switching from other developmental disabilities to PDD, service availability, and awareness of autistic spectrum disorders in both the lay and professional public [4].

The prevalence of ASD was 18.5 per 1,000 (one in 54) children aged eight years, and ASD is about 4.3 times as prevalent among males as among females. The prevalence varied from 13.1 in Colorado to 31.4 in New Jersey. The Prevalence estimates were similar for non-Hispanic white, non-Hispanic black, and Asian children (18.5, 18.3, and 17.9, respectively) but less in Hispanic children (15.4). In children with ASD for whom data on intellectual or cognitive functioning were available, 33% were classified as having an intellectual disability (intelligence quotient [I.Q.] ≤70). This percentage was higher among females than males.

Autism affects the a communicates with and relates to other people and how people make sense of the world around them. The etiology of autism is unknown, but the core idea is that the brain of someone with Autism functions differently, receiving, and processing information in a different way [5-10].

Autism is a condition that means there are lots of different ways that Autism can affect individuals. Autism manifests in many ways. Everyone is unique with their abilities, talents, challenges, and symptoms. In the general population, many people have comorbidities (i.e., more than one health condition at any one time). People with Autism are the same and can have other conditions, such as a learning disability, mental health challenges, OCD, ADHD, and Dyspraxia [11,12].

Types of Autism Spectrum Disorder (ASD)

The "umbrella" heading is a Pervasive Developmental Disorder (PDD).

Autism is one of the 5 PDDs. All have commonalities in communication, and social deficits Differ in terms of severity.

Autistic disorder is Impairments in social interaction, communication, and imaginative play. Apparent before age 3. Also includes stereotyped behaviors, interests, and activities. Asperger's Disorder is impairments in social interactions and the presence of restricted interests and activities. No clinically significant general delay in language. Average to above-average intelligence 3. Pervasive Developmental Disorder. It is often referred to as atypical Autism. It used when a child does not meet the criteria for a specific diagnosis, but there is severe and pervasive impairment in specified behaviors Rett's Disorder is a progressive disorder that has only occurred in girls to date. Period of normal development and then the loss of previously acquired skills. Also, loss of purposeful use of hands, which is replaced by repetitive hand movements Childhood Disintegrative Disorder is beginning at the age of 1-4 years. It has normal development for at least the first two years. It is associated with significant loss of previously acquired skills [4,13].

Diagnosis of ASD

Autism was not included as a diagnostic category until the publication of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) in 1980(Association, 1980). Additional diagnostic refinements included the addition of pervasive developmental disorder not otherwise specified (PDD-NOS) in 1987 and the inclusion of Asperger's syndrome in DSM-IV (Association, 2000).

The DSM diagnosis of ASD was further revised with the recent publication of DSM-5. ASD phenotype diagnoses of the autistic disorder, Asperger's syndrome, atypical Autism, and PDD-NOS were replaced with one diagnosis: ASD. Additionally, the three ASD domains included in DSM-IV and International Classification of Diseases, Tenth Edition (ICD-10) (social reciprocity, communication, and restricted and repetitive behaviors) were collapsed into two domains: 1) social communication/interaction and 2) restricted and repetitive behaviors, with the evidence required of persistent symptoms that cause functional impairment (current or historical) in these two domains. Furthermore, abnormalities in sensory reactivity were added to the restricted/repetitive behavior domain. Importantly, DSM-5 acknowledges that, although symptoms must begin in early childhood, they may become more recognizable in later life with increasing social demands [13]. The latter may be particularly relevant for individuals whose symptoms may present a different pattern or become more evident with adult life (e.g., females or young people transitioning from a structured school environment to the less-structured college) [14].

The diagnoses of childhood autism, Asperser's syndrome, atypical autism, and PDD-unspecified are still. Autism is a lifelong developmental condition that affects the brain and its functions. Autism affects the person and the people around them like their family, friends, and careers.

There are scales used for diagnosis of Autism as Gilliam Autism Rating Scale Arabic version: An assessment of the severity of Autism using the Gilliam autism rating scale (GARS) Arabic version: This test was used for diagnosis and assessment of the severity of autistic features for ages 3-22 years. It consists of 56 items, subdivided into four subscales: communication, social interaction, stereotyped behaviors, development, and the total score [15,16]. The Arabic version has been validated with good reliability and validity and used in many studies before [17]. The lower the scores are, the worse the condition is.

The Vineland Adaptive Behavioral Scale (VABS) will assess patients' adaptive functions [18]. The test includes four subdomains (communication, social skills, daily living, and motor skills) and a composite adaptive behavioral score.

Aetiology

ASD is not a single disorder. It is now broadly considered a multifactorial disorder resulting from genetic and non-genetic risk factors as abnormalities in brain development, neurochemistry, and interaction.

Genetic Influence

Autism is a highly heritable disorder, with inherited genetic risk sets being associated with sub-threshold autistic traits and the clinical ASD phenotype in extensive twin studies, supporting the notion that clinical disorders exist as the quantitative extreme of a continuum. As in other psychiatric disorders, common genetic variants distributed along the genome seem to increase the risk modestly, while rare genetic variants, de novo or in close ancestry, seem to increase individual risk significantly. Many genes have been shown to carry a risk for Autism, with no single locus accounting for more than 1% of the cases. Also, identical variations have been shown to carry large effects for a wide range of outcomes, including ASD and other developmental disorders [19]. A diagnosable medical condition, cytogenetic abnormalities, or single-gene defects can be found in 10–25% of complex Autism cases. Essential Autism is characterized by an absence of dysmorphic features, a more frequent family history of Autism is more frequently diagnosed in males, and the etiology is very rarely found [20].

General recurrence rates of Autism in the same family are in the range of 10-18%. However, essential Autism has a higher recurrence rate (up to 35%). In addition to ASD in relatives, quantitative analysis of autistic traits and language disorders shows that around 20-25% of siblings have predominantly pragmatic language deficits. Many studies have used twins and more distant relatives to establish the contribution of genetic factors to the etiology of Autism and ASD [21].

The three major twin studies examining the concordance of strictly defined Autism between monozygotic (M.Z.) twins have yielded similar figures of around 60%.

Early twin studies reported concordance for D.Z. Twins of 10-15%. However, the most extensive population-based twin study to date has shown concordance rates of 21-36% in D.Z. Twins, using DSM-IV diagnostic criteria for ASD (known to be associated with increased prevalence rates of ASD). The shared environment was reported in this study to account for 55 and 58% of the variance in liability in strict Autism and ASD, respectively [22].

Different studies identify single-nucleotide polymorphisms (SNPs) and other common genetic variants in DNA that may be associated with a disease or trait by investigating the entire genome using an unbiased hypothesis-free search. These studies have identified more than 100 genes and 40 genomic regions related to ASD or ASD traits, each with a weak effect [23]. Candidate genes for ASD have been identified, but their contribution to pathogenesis remains unclear in many cases. Current genetic studies point towards ASD risk genes associated with proteins involved in: Synaptic mechanisms (including NRXNs, NLNGs, CNTN3/4, CNTNAP2, and SHANK3); Genes associated with neuronal migration, Growth and differentiation abnormalities (i.e., gene products of EN2 or MET, PTEN, TSC1/2, CTNTAP2, FMR1). Genes involved in proteins related to excitatory and inhibitory neurotransmission (GABA and glutamate receptors such as GRIN2B) or membrane ion channels (SCN2A) Additionally, genes coding for proteins involved in cell regulation (DYRK1A) or structure (KANTAL2), An action at the level of the cell nucleus (DNA binding proteins POGZ or chromatin modifiers CHD8) have been recently discovered [24].

Neuropathology

The abnormal mini-columnar structure in the neocortex seems to be a common finding. Cerebellar abnormalities are also common and include abnormal volumes (although generally proportional to brain volume) [25]. They reduced the number and size of Purkinje neurons in the vermis and hemispheres—molecular defects in posterior regions [26]. Postmortem tissues provide an opportunity to study gene expression. GABAA subunit expression is decreased in the Superior frontal gyrus, parietal cortex, and Cerebellum (Amaral et al., 2008). It is important to note that most neuropathology findings come from autistic children with mental retardation and a high percentage of epilepsy [20,27].

Brain Structure and Function

Neuroimaging Studies

Brains of a significant number (around 25-30%) of autistic children increase excessively in size .Enlargement (metabolic hypo-function) seems to be particularly marked in frontal regions, the amygdala and cerebellum [25]. Increased number, size or myelin content of neuroglia, increased elaboration of neuronal dendrites, axons or decreased pruning or inflammatory responses, Functional MRI and neurophysiological studies., Autism as a ''dis-connectivity'' disorder focuses more on ; Impairment of specific brain networks instead of specific brain regions [28].

This ''dis-connectivity" pattern lacks effective integration of distributed brain regions disruption in the modulation of brain function concerning changing demands. The pattern of activation and timing or synchronization between different brain regions is the most impaired feature. Only in a few fMRI tasks, such as information processing tasks involving face and object recognition, there seems to be an atypical activation location [25,27,28].

Redox System and Mitochondrial Dysfunction

Children with autism have reduced antioxidant capacity and may suffer from chronic oxidative stress. Increased oxidative stress has been reported. Plasma reactive oxygen species (ROS) and antioxidant activity are disturbed in autism spectrum disorders than healthy controls [29] The abnormalities in methionine and glutathione metabolism in autistic children are shared by their parents, suggesting a genetic origin for these abnormalities [30].

Immune Dysregulation

Several studies have shown how immune factors such as TNFa, IFNg, IL-1b, and IL-12 are increased in the peripheral blood of ASD patients [31]. Pro-inflammatory cytokines have also been shown to be increased in the cerebral spinal fluid (CSF) of autistic patients [32]. Besides, studies using protein arrays to explore the cytokine profile in the postmortem brains of autistic patients showed evidence of a pro-inflammatory condition [31].

Oxytocin and other Social Neuropeptides

In subjects with ASD, low levels of oxytocin have been reported compared with controls, and specific SNPs of the oxytocin receptor gene be associated with Autism in different populations [33]. Preliminary clinical studies show the adjunctive effect of oxytocin in some psychotherapeutic interventions targeting social abilities in ASD patients [34].

Other Biomarkers

Elevated platelet serotonin levels have been repeatedly found in about 30% of the children with autism [35]. Urine amino acid and organic acid testing are one of the per-protocol medical workups in many clinics evaluating children with Autism, in order to search for treatable metabolic disorders associated with the ASD phenotype [36]. The plasma levels of multiple growth factors (G.F.) include endothelial G.F., platelet-derived G.F., hepatocyte G.F., and epidermal G.F., and reduced plasma levels have been reported in different studies (generally with no clinical correlates [35,37].

Environmental Factors

Studies link autism to exposure (thalidomide, misoprostol, valproic acid) early in pregnancy; Maternal Influenza, rubella, and cytomegalovirus, etc [38]. Also, diabetes, the organophosphate insecticide, zinc deficiency, abnormal melatonin synthesis, stress hormones, psychological stress, and prenatal and perinatal stress [20]. Environmental factors such as pesticides, solvents, and attractive candidates explain part of the increase in ASD [4]. These environmental effectors account for a minimal number of cases. However, they are illustrative of how external effectors (in likely interaction with genetic vulnerabilities) can initiate a path-physiological cascade starting very early in prenatal life and ending with an autistic phenotype [20,38].

Treatment Modalities

Various educational and behavioral treatments have been the mainstay of the management of ASD. Most experts agree that the treatment for ASD should be individualized. Treatment of disabling symptoms such as aggression, agitation, hyperactivity, inattention, irritability, repetitive and self-injurious behavior may allow educational and behavioral interventions to proceed more effectively [39].

Individualization and Early Intervention

Most experts agree that the treatment for ASD should be individualized. There is no single best treatment package for all children with ASD. Early intervention is essential. Autism society guidelines include many parents' questions that can ask before potential treatment options as (treatment harm, response, failure of treatment [1].

Applied Behavioral analysis (Lovaas model)

Ivar Lovaas and his colleagues develop it. One-on-one child-teacher interaction for 40 hours/ weak The goal of behavioral management is to reinforce desirable behavior and reduce undesirable ones. An effective treatment program

will build on: the child's interests offer a predictable schedule, teach tasks as a series of simple steps actively to engage the child's attention, Regular reinforcement, and parents share [1]. The Lovaas Approach is a form of Applied Behavioral Analysis used in early intervention programs for children who have developmental delays or who have been identified as autistic. The program, created by Ole Ivar Lovaas, is derived from work done by B.F. Skinner in the 1930s. The goal is to begin intervention with children as young as two to help them gain communication abilities and skills in education and daily living activities. The intervention consists of breaking skills down into the simplest components and rewarding children positively and then "generalizing" the skills into a natural environment [40].

The first step is establishing a rapport with the children. Children need to learn the verbal language, if possible. Parental involvement is crucial for the continuity of treatment at home. Another component of this approach is encouraging the child to imitate other children to develop social skills. The Lovaas approach of working with autistic and developmentally delayed children is based on scientific principles. Progress is continually measured and adapted as children age. The motivating rewards differ with each child, as does the program.

Medical management includes typical antipsychotics, atypical antipsychotics, antidepressants, selective serotonin reuptake inhibitors, α2-adrenergic agonists [41], β-adrenergic antagonist, mood stabilizers, and anticonvulsants [41].

So far, there has been no agent which has been proved effective in social communication [42]. A major factor in the choice of pharmacologic treatment is awareness of specific individual physical, behavioral or psychiatric conditions comorbid with ASD, such as obsessive-compulsive disorder, schizophrenia, mood disorder, and intellectual disability [43].

Anxiety and Depression

The selective serotonin reuptake inhibitors (SSRI's) are medications most prescribed for symptoms of anxiety and depression. Fluoxetine (Prozac) has been approved by FDA for depression and OCD in children age 7 and more. Fluvoxamine approved for age 8 and more. Sertraline approved for age 6 and more. Treatment with theses medication can be associated with decreased frequency of repetitive, ritualistic behavior and improvement in eye contact and social contacts.

Antidepressants were the most commonly used agents followed by stimulants and antipsychotics. The high prevalence of comorbidities is reflected in the rates of psychotropic medication use in people with ASD.

Behavioral Problems

Antipsychotics effectively treated the repetitive behaviors in children with ASD; however, there was not sufficient evidence on the efficacy and safety in adolescents and adults [12,44,45]. Old antipsychotic such as haloperidol was found in more than study to effect treatment in ASD. New atypical antipsychotics were recorded in clinical trials for treating severe behavioral problems as risperidone.

There are also alternative options, including the opiate antagonist, immunotherapy, hormonal agents, megavitamins, and other dietary supplements [12].

Seizure

One in four persons with Autism present with seizures. Most often in those who have low I.Q. or are mute. Only a few anti-epileptic drugs (AEDs) have undergone carefully controlled trials in ASD, but these trials examined outcomes other than seizures. Several lines of evidence point to valproate, lamotrigine, and levetiracetam as the most effective and tolerable AEDs for individuals with ASD. Limited evidence supports the use of traditional non-AED treatments, such as the ketogenic and modified Atkins diet, multiple subpial transections, immunomodulation, and neurofeedback treatments. Although specific treatments may be more appropriate for specific genetic and metabolic syndromes associated with ASD and seizures, few studies have documented treatments' effectiveness for specific syndromes. Limited evidence supports L-carnitine, multivitamins, and N-acetyl-L-cysteine in mitochondrial dis-ease and dysfunction, folinic acid in cerebral folate abnormalities early treatment with vigabatrin in tuberous sclerosis complex. Finally, there is limited evidence for several novel treatments, particularly magnesium with pyridoxine, omega-3 fatty acids, the gluten-free casein-free diet, and low-frequency repetitive transcranial magnetic stimulation. Zinc and L-carnosine are potential novel treatments supported by primary research but not clinical studies. This review demonstrates the wide variety of treatments used to treat seizures in individuals with ASD and the striking lack of clinical trials performed to support the use of these treatments. Additional studies concerning these treatments for controlling seizures in individuals with ASD are warranted [46,47]. These individuals have severely progressed disease and multiple comorbidities. A child with ASD may not respond in the same way to medications as typically developing children. So, it is essential to deal with a doctor with experience with Autism. A child should be

monitored closely while taking medications. A doctor will prescribe the lowest dose possible to be effective.

However, the autistic symptoms remain refractory to medication therapy in some patients causing a decreased quality of life [41].

Dietary intervention in Autism

It has been suggested that nutritional factors play a significant role. Significantly lower levels of various nutrients in blood have been observed in autistic children, including low levels of zinc, selenium, vitamin D, and omega-3 fatty acids [48].

Ketogenic diet

Currently, a variety of nutritional interventions are in use, including gluten and casein-free diet (GFCF), ketogenic diet, yeast-free diet, restriction of food allergens, probiotics, and dietary supplementation with vitamins A, C, B6, folic acid, B12, minerals like magnesium and omega-3 fatty acids [49].

Gluten And Casein-Free Diet

Gluten and casein-free diet: This diet calls for the complete elimination of both gluten and casein, which is found in wheat, rye, barley, and oats, as well as casein, the protein in milk and all milk products is proposed that increased intestinal permeability, also referred to as "leaky gut syndrome," allows these peptides to cross the intestinal membrane and cross the blood-brain barrier through entry into the bloodstream, thereby affecting the endogenous opiate system and neurotransmission in the nervous system [50].

The ketogenic diet was first introduced as a therapeutic method to reduce the number and intensity of epileptic seizures. However, it has been reported that also, the ketogenic diet is beneficial for mental behavior and hyperactivity. In the classic ketogenic diet, also known as the long-chain triglyceride diet, fat provides the majority of energy, protein is based on minimum daily requirements, and carbohydrates are severely restricted [51-53]. It is hypothesized that autistic behavior is associated with a disturbance in glucose metabolism, particularly mitochondrial energy production, leading to an excess of reduced nicotinamide adenine dinucleotide (NADH) or a lack of nicotinamide dinucleotide (NAD) [51].

It is thought that the application of a ketogenic diet would produce an improved mitochondrial function by sparing NAD, which will be consumed in the oxidation of glycolytic substrates [54].

Feingold Diet

This diet is based on the benefit of a food-restriction diet for attention deficit and hyperactivity disorder. Scientifically undocumented behavioral improvements after the elimination of food colors and flavors have been reported. According to Dr. Feingold's hypothesis elimination of food, additives resulted in some cases in a dramatic decline in hyperactive symptoms (Feingold, 1985). At this time, no rigorous randomized trials have been conducted to evaluate the efficacy of the Feingold diet for easing the symptoms of ASD [55].

Antioxidant diets

Antioxidant diets have gained the attention of some investigators who are concerned about oxidative stress in Autism and related conditions. Commonly recommended foods are fresh fruits and vegetables, cooked legumes, and whole grains [56,57]. The superfoods recommended on this type of diet are broccoli, Brussels sprouts, berries like blueberries, and Goji berries. Moderate servings of animal products such as lean meat are allowed. This dietary pattern is part of a healthy diet recommended for the general population, but it has not been tested to reduce ASD [56].

Adults with an Autism Spectrum Disorder

Although early ASD research focused primarily on children, there is increasing recognition that ASD is a lifelong neuro-developmental disorder. However, although the health and education services for children with ASD are relatively well established, service provision for adults with ASD is in its infancy and needs more studies. There is a lack of health services research for adults with ASD, including identification of comorbid health difficulties, rigorous treatment trials (pharmacological and psychological), development of new pharmacotherapies, investigation of transition and aging across the lifespan, and consideration of sex differences and the views of people with ASD [14].

Some adults with ASD, especially those with high functioning autism, can work in mainstream jobs. Communication and social problems often cause difficulties in many areas of life. They will continue to need encouragement and moral support.

The health services research for adults with ASD is urgently warranted. Research is required to understand better adults' needs with ASD, including health, aging, service development, therapy options across lifespan, sex, and the views of people with ASD. Additionally, recent international

legislative efforts to raise awareness of ASD and service provision for adults with ASD are to be determined. Future researches could help in identifying high-quality, evidence-based, and cost-effective care models. Besides, future health services research is also required at the beginning and end of adulthood, including an improved transition from youth to adult health care and increased understanding of aging and health in older adults with ASD [14].

References

1. Park HR, Lee JM, Moon HE, Lee DS (2016) A Short Review on the Current Understanding of Autism Spectrum Disorders. Exp Neurobiol 25(1): 1-13.
2. Willsey AJ, State MW (2015) Autism spectrum disorders: from genes to neurobiology. Curr Opin Neurobiol 30: 92-99.
3. HA (2014) Autism and Asperger Syndrome. Translation and annotation of "autistic psychopathy" in childhood, ed. F. U. 1991, Cambridge University Press: Cambridge, 37-92.
4. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S (2012) Global prevalence of autism and other pervasive developmental disorders. Autism Res 5(3): 160-179.
5. Yenkoyan K, Artem Grigoryan, Katarine Fereshetyan, Diana Yepremyan (2017) Advances in understanding the pathophysiology of autism spectrum disorders. Behav Brain Res 331: 92-101.
6. Barros DM (2020) Online dating, reproductive success and the rise autism spectrum disorder prevalence. Med Hypotheses 140: 109679.
7. May T, Brignell A, Williams K (2020) Autism Spectrum Disorder Prevalence in Children Aged 12-13 Years From the Longitudinal Study of Australian Children. Autism Res 13(5): 821-827.
8. Delobel-Ayoub M, Saemundsen E, Gissler M, Ego A, Moilanen I (2020) Prevalence of Autism Spectrum Disorder in 7-9-Year-Old Children in Denmark, Finland, France and Iceland: A Population-Based Registries Approach Within the ASDEU Project. J Autism Dev Disord 50(3): 949-959.
9. Qiu S, Yuping Lu, Yan Li, Jikang Shi, Heran Cui (2020) Prevalence of autism spectrum disorder in Asia: A systematic review and meta-analysis. Psychiatry Res 284: 112679.
10. Melo C, Luís Ruano, Joana Jorge, Tiago Pinto Ribeiro, Guiomar Oliveira (2020) Prevalence and determinants of motor stereotypies in autism spectrum disorder: A systematic review and meta-analysis. Autism 24(3): 569-590.
11. Wong J, Maree J Webster, Hope Cassano, Cynthia S Weickert (2009) Changes in alternative brain-derived neurotrophic factor transcript expression in the developing human prefrontal cortex. Eur J Neurosci 29(7): 1311-1322.
12. Warren Z, Melissa L McPheeters, Nila Sathe, Jennifer H Foss-Feig, Allison Glasser (2011) A systematic review of early intensive intervention for autism spectrum disorders. Pediatrics 127(5): e1303-e1311.
13. Mugzach O, Mor Peleg, Steven C Bagley, Stephen J Guter, Edwin H Cook (2015) An ontology for Autism Spectrum Disorder (ASD) to infer ASD phenotypes from Autism Diagnostic Interview-Revised data. J Biomed Inform 56: 333-347.
14. Murphy CM, C Ellie Wilson, Dene M Robertson, Christine Ecker, Eileen M Daly (2016) Autism spectrum disorder in adults: diagnosis, management, and health services development. Neuropsychiatr Dis Treat 12: 1669-1686.
15. Gilliam JE (2001) Gilliam Asperger's Disorder Scale, TX: Pro-Ed: Austin.
16. Gilliam JE (2014) Gilliam Autism Rating Scale, TX: Pro-Ed: Austin.
17. Abdelrahman ME, Gilliam HM (2004) Autism Rating Scale Arabic version. Dar El-Sahab press: Cairo.
18. Sparrow SS, Balla AD (2005) Vineland adaptive behavior scales, in American Guidance Service, MN: Circle Pines.
19. Li X, Zou H, Brown WT (2012) Genes associated with autism spectrum disorder. Brain Res Bull 88(6): 543-552.
20. Parellada M, Penzol MJ, Pina L, Moreno C (2014) The neurobiology of autism spectrum disorders. Eur Psychiatry 29(1): 11-19.
21. Constantino JN, Yi Zhang, Thomas Frazier, Anna M Abbacchi, Paul Law (2010) Sibling recurrence and the genetic epidemiology of autism. Am J Psychiatry, 167(11): 1349-1356.
22. Weintraub K (2011) The prevalence puzzle: Autism counts. Nature 479(7371): 22-24.
23. Rossignol E (2011) Genetics and function of neocortical GABAergic interneurons in neurodevelopmental disorders. Neural Plast 2011: 649325.

24. Hussman JP (2011) A noise-reduction GWAS analysis implicates altered regulation of neurite outgrowth and guidance in autism. Mol Autism 2(1): 1.

25. Courchesne EE, Redcay, Kennedy DP (2004) The autistic brain: birth through adulthood. Curr Opin Neurol 17(4): 489-496.

26. Fatemi SH, Timothy D Folsom, Teri J Reutiman, Paul D Thuras (2009) Expression of GABA(B) receptors is altered in brains of subjects with autism. Cerebellum 8(1): 64-69.

27. Amaral DG, Schumann CM, Nordahl CW (2008) Neuroanatomy of autism. Trends Neurosci 31(3): 137-145.

28. Courchesne EK, Campbell K, Solso S (2011) Brain growth across the life span in autism: age-specific changes in anatomical pathology. Brain Res 1380: 138-145.

29. James SJ, Stepan Melnyk, Stefanie Jernigan, Oleksandra Pavliv, Timothy Trusty (2010) A functional polymorphism in the reduced folate carrier gene and DNA hypomethylation in mothers of children with autism. Am J Med Genet B Neuropsychiatr Genet 153B(6): 1209-1220.

30. James SJ, Paul Cutler, Stepan Melnyk, Stefanie Jernigan, Laurette Janak (2004) Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. Am J Clin Nutr 80(6): 1611-1617.

31. Vargas DL, Caterina Nascimbene, Chitra Krishnan, Andrew W Zimmerman, Carlos A Pardo (2005) Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol 57(1): 67-81.

32. Thomas RH, Melissa M Meeking, Jennifer R Mepham, Lisa Tichenoff, Fred Possmayer (2012) The enteric bacterial metabolite propionic acid alters brain and plasma phospholipid molecular species: further development of a rodent model of autism spectrum disorders. J Neuroinflammation 9: 153.

33. Yamasue H, Jason R Yee, René Hurlemann, James K Rilling, Frances S Chen (2012) Integrative approaches utilizing oxytocin to enhance prosocial behavior: from animal and human social behavior to autistic social dysfunction. J Neurosci 32(41): 14109-14117.

34. Wu S, Meixiang Jia, Yan Ruan, Jing Liu, Yanqing Guo (2005) Positive association of the oxytocin receptor gene (OXTR) with autism in the Chinese Han population. Biol Psychiatry 58(1): 74-77.

35. Schmidt RJ, Robin L Hansen, Jaana Hartiala, Hooman Allayee, Linda C Schmidt (2011) Prenatal vitamins, one-carbon metabolism gene variants, and risk for autism. Epidemiology 22(4): 476-485.

36. Sacco R, Curatolo P, Manzi B, Militerni R, Bravaccio C (2010) Principal pathogenetic components and biological endophenotypes in autism spectrum disorders. Autism Res 3(5): 237-252.

37. Sacco R, Lenti C, Saccani M, Curatolo P, Manzi B (2012) Cluster analysis of autistic patients based on principal pathogenetic components. Autism Res 5(2): 137-147.

38. PJ L (2010) What causes autism? Exploring the environmental contribution. Curr Opin Pediatr 22: 219-225.

39. Posey DJ, McDougle CJ (2001) Pharmacotherapeutic management of autism. Expert Opin Pharmacother 2(4): 587-600.

40. Rogers SJ, Vismara LA (2008) Evidence-based comprehensive treatments for early autism. J Clin Child Adolesc Psychol 37(1): 8-38.

41. Adler BA, Wink LK, Early M, Shaffer R, Minshawi N (2015) Drug-refractory aggression, self-injurious behavior, and severe tantrums in autism spectrum disorders: a chart review study. Autism 19(1): 102-106.

42. Farmer CA, Thurm, Grant P (2013) Pharmacotherapy for the core symptoms in autistic disorder: current status of the research. Drugs 73(4): 303-314.

43. Kerbeshian J, Burd L (2001) Pharmacotherapy of autism: A review and clinical approach. J Dev Phys Disabil 13: 199-228.

44. Krishnaswami S, McPheeters ML, Veenstra-Vanderweele J (2011) A systematic review of secretin for children with autism spectrum disorders. Pediatrics 127(5): e1322-e1325.

45. McPheeters ML, Warren Z, Sathe N, Bruzek Jl, Krishnaswami S (2011) A systematic review of medical treatments for children with autism spectrum disorders. Pediatrics 127(5): e1312-e1321.

46. Frye RE, Rossignol D, Casanova MF, Brown GL, Martin (2013) A review of traditional and novel treatments for seizures in autism spectrum disorder: findings from a systematic review and expert panel. Front Public Health 1:31.

47. Richards C, Oliver C, Nelson L, Moss J (2012) Self-injurious behaviour in individuals with autism spectrum disorder and intellectual disability. J Intellect Disabil Res

56(5): 476-489.

48. Elder JH (2008) The gluten-free, casein-free diet in autism: an overview with clinical implications. Nutr Clin Pract 23(6): 583-588.

49. Elder JH, Kreider CM, Schaefer NM, Laosa MB (2015) A review of gluten- and casein-free diets for treatment of autism: 2005-2015. Nutr Diet Suppl 7: 87-101.

50. M CK (2010) The review of most frequently occurring medical disorders related to aetiology of autism and the methods of treatment. Ac. Acta Neurobiol Exp 70(2): 141-146.

51. Kossoff EH, Zupec-Kania BA, Rho JM (2009) Ketogenic diets: an update for child neurologists. J Child Neurol 24(8): 979-988.

52. Kossoff EH (2009) The ketogenic diet: it's about 'time'. Dev Med Child Neurol 51(4): 252-253.

53. Kossoff EH, Rho JM (2009) Ketogenic diets: evidence for short- and long-term efficacy. Neurotherapeutics 6(2): 406-414.

54. Evangeliou A, Vlachonikolis I, Mihailidou H, Spilioti M, Skarpalezou A, et al, (2003) Application of a ketogenic diet in children with autistic behavior: pilot study. J Child Neurol 18(2): 113-118.

55. Feingold B (1985) Why your child is hyperactive. Random House: New York.

56. Srinivasan PA (2009) review of dietary interventions in autism. Ann Clin Psychiatry 21(4): 237-247.

57. Jeep R, Couey R, ES P (2018) The super antioxidant diet and nutrition guide. 2008, Charlottesville, VA: Hampton Roads Publishing Company.