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Short Review

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Insights into the autistic disorder and potential therapeutic approaches

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Abstract

Autism and autism spectrum disorders (ASDs) such as Rett syndrome and Asperger syndrome are enigmatic and complex neurodevelopmental disorders, thought to have originated in particular interactions of genetic and environmental factors. Despite the extensive research, exact mechanism of pathogenesis is not still completely understood. ASDs are characterized by deficits and abnormalities in communication and social interactions, besides repetitive and stereotypic verbal/nonverbal behaviors. There are no effective drugs for the treatment of these conditions and as the frequency of ASDs in the children has risen over the last decade, further studies will be needed to better address the treatment. In this brief review we discuss the etiology of autism and possible novel approaches for its management in the near future .

Key words: Autism, Autism spectrum disorders, Pervasive developmental disorders, Autism treatment

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1. Introduction

ASDs are a group of neurodevelopmental conditions, which include autism, Rett's disorder Asperger's syndrome, Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS ; also called atypical autism) and childhood disintegrative disorder. Autistic disorder is the most prevalent of a subset of conditions that are classified under the umbrella of pervasive developmental disorder (PDD). Severity can be different in autism, ranging from mild to disabling and is accompanied by mental retardation in three out of four patients (Ichim et al., 2007; Rapin 1997; Rapin and Tuchman 2008).

1.1 Etiology

The exact etiologies of autism remain unknown. Probably ASDs occur due to a combination of different factors (Pubmed health 2012), including altered neurodevelopment in the early prenatal life, cerebellar alterations with a decreased number of Purkinje cells (Benvenuto et al., 2009), inflammation of the brain (Ratajczak, 2011), mutations and deletions of specific genes (Landrigan, 2010), environmental exposures e.g. exposing to air pollutants, heavy metals and organophosphate insecticides (Siniscalco et al., 2012). The possible roles of oxidative stress and toxic metal burden, decreased methylation capacity (Rossignol and Frye, 2012), abnormal biochemical markers and molecular abnormalities arising from mitochondrial defects (Dhillon et al., 2011; Rossignol and Frye, 2012), intestinal pathophysiology such as impairment in gut development (White, 2003), autoantibodies which target brain proteins, changes in immune responses (Goines and Van de Water, 2010), vaccine sensitivity and mercury poisoning (Gerber and Offit, 2009) have been suggested in this regards.

1.2 Risk factors

Certain factors increase the children's risk for autism, which include, child's gender it means boys are three times more likely than girls in receiving the diagnosis, family history, several medical conditions (i.e. fragile X syndrome, tuberous sclerosis, Tourette syndrome and epilepsy), increased maternal and paternal age at the birth, gestational bleeding, medication use in pregnancy, gestational diabetes and obstetric conditions such as newborn hypoxia and low-birth-weight (prenatal, natal and post natal risk factors) (El-Baz et al., 2011; Gardener et al., 2009; Kolevzon et al., 2007; Mayoclinic 2012).

1.3 Symptoms

Autistic children generally have some problems in three main areas of development, social interactions, language and behavior but these symptoms vary widely in diagnosed patients (Mayoclinic 2012). Some common symptoms may include significant problems in facial expressions, body posture and eye contact, failure to make friends, lack of empathy, delay/lack in learning to talk. Problems in starting or continuing a conversation, echolalia (Webmd 2012), insisting on sameness, resisting changes, ritualistic behaviors, odd plays, abnormal posture (toe walking), self-injurious behavior, extreme under-activity or over-activity, abnormal patterns in eating or sleeping, not responding to the normal teaching, preoccupation with parts of the objects, repetitive movements and no fear in dangerous situations (Emedicine health 2012; Johnson and Myers, 2007). Autism can occur at all intelligence levels. In fact about 75% of autistic patients have an intelligence quotient below average, 25% show an average or above average intelligence and approximately 10% of autistic patients exhibit savant abilities that means extraordinary musical, artistic and memory skills (Pring et al., 2012; Treffert, 1999; Treffert, 2009).

1.4 Diagnosis

ASDs may go unrecognized especially in children who are mildly affected or when they are masked by other debilitating physical or mental conditions. There are certain symptoms that indicate the necessity of further evaluation by an expert such as no babbling and pointing by age 1, no single words by 16 months or two-word phrases by age 2, not a good eye contact, excessive lining up of objects, no response to the name, poor ability to make friends, absence of social play. A questionnaire or other screening instrument like Autism Diagnostic Observation Schedule (ADOS) may be used in order to collect information about the child's development. Several physical assessments and laboratory tests such as hearing testing, testing for lead poisoning, magnetic resonance image (MRI) and electroencephalograph (EEG) also can be used for more accurate diagnosis. ASD diagnosis will often be based on the diagnostic and statistical manual IV (DSM-IV) book (Ninds 2012; Risi et al., 2006; You et al., 2011) .

1.5 Biomarkers

Some biomarkers in ASDs include complete blood count, comprehensive metabolic panel (which includes liver and kidney testing), magnesium, zinc and ferritin serum levels, cholesterol and testosterone levels, hypothyroidism, oxidative stress biomarkers such as reduced and oxidized glutathione levels and carnitine profile. Methylation capacity and trassulfuration biomarkers, immune biomarkers such as vaccine titers and serum autoantibodies to the brain endovasculature, gastrointestinal and heavy metal biomarkers (Bradstreet et al., 2012; Geiera et al., 2009).

2. Treatment

An early and appropriate treatment protocol is greatly crucial and will improve the outlook and quality of life for the patients (Ninds 2012; Pubmed health 2012). A wide variety of therapies are available, including antipsychotics, antidepressant, stimulants, anticonvulsants, alpha-2 adrenergic agonists and buspirone. Other treatment strategies include applied behavior analysis (ABA) (Axelrod et al., 2012), treatment and education of autistic and related communication handicapped children (TEACCH) (Panerai et al., 2009), occupational therapy, individual and family psychotherapy and sensory integration interventions (Koenig and Levine, 2011; Webmd 2012). Chiropractic care, hyperbaric oxygen therapy, play therapy, acupuncture , neurofeedback, physical therapy, speech-language therapy and vision therapy are the other effective treatment approaches in autistic disorders (Alcantara et al., 2011).

Nutritional interventions and dietary supplements are effective in controlling signs and symptoms of Autism. For example omega-3 fatty acids, gluten/casein-free diets, special carbohydrate diets, multivitamins and probiotics (Geraghty, 2010) have been recommended in this regard. However, more research is needed to ensure the effectiveness of some options mentioned above, medical treatments are considered as adjuncts to the educational and behavioral interventions but the patients shall receive both pharmacologic and complementary-alternative medicine therapies (Huffman et al., 2011).

3. New therapeutic targets

Finding the novel approaches to treat ASDs is a very active area of research. Herein, we mentioned several new therapeutic targets which show great promises for the future.

3.1 Personalized therapy through mesenchymal stem cells:

It will be due to an immunomodulatory

mechanism of action (Hoogduijn et al., 2010; Momin et al., 2010; Siniscalco et al., 2012).

3.2 Intravenous immunoglobulin (IVIG):

As the role of autoimmunity and immunological connection has been widely accepted for autism, there is a rational thought for the therapeutic use of IVIG (Gupta et al., 2010).

3.3 Glycine site antagonists on NMDA (N-methyl-D-aspartate) receptor:

They can be tested as a new approach, based on the hypofunction of GABAergic system and glutamate toxicity hypotheses (Ghanizadeh, 2011).

3.4 Modulation of neurotensin and its receptors:

Neurotensin is known to increase NMDA mediated glutamate signaling, activates inflammatory processes and will lead to apoptosis as well as brain damage (Ghanizadeh, 2010).

3.5 Transplantation of c-Kit+ cells:

They will intensify the expression of GLT-1 (a transporter that plays an important role for glutamate removal and keeps the glutamate synaptic concentration low in order to prevent excitotoxicity) (Ghanizadeh, 2011).

3.6 Modulation of oxytocin system:

This modulation can improve social behavior and social communication/interaction in autistic patients (Andari et al., 2010; Guastella et al., 2010; Modi and Young, 2012; Sala et al., 2011).

3.7 Targeting oxidative pathways:

Targeting oxidative pathways is also suggested by Villagonzalo et al. in 2010 .

3.8 Targeting gut-to-brain connections:

Targeting gut-to-brain connections is another approach which is suggested by de Theije et al. in 2011.

These are examples of new management of ASDs, but further studies to explore the effectiveness of these novel therapeutic strategies are needed.

4. Conclusion

Taken together, autism is a condition that some of its aspects are not completely clear. The frequency of ASDs is increasing and the disorders indeed are not still fully treatable. For this reason, the use of unconventional treatment methods seems necessary. In this review we discussed causes, symptoms and diagnosis of the autistic disorder, available treatment options and possible directions for the future research.

Conflict of interests : None declared.

5. References

Alcantara J, Alcantara JD, Alcantara J. A systematic review of the literature on the chiropractic care of patients with autism spectrum disorder. Explore (NY). 2011; 7:384-90

Andari E, Duhamel JR, Zalla T, et al. Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. Proc Natl Acad Sci U S A. 2010; 107: 4389-94

Axelrod S, Kates McElrath K, Wine B. Applied behavior analysis: autism and beyond . Behav. Intervent. 2012; 27:1-15

Benvenuto A, Moavero R, Alessandrelli R, et al. Syndromic autism: causes and pathogenetic pathways. World J Pediatr. 2009; 5:169-76

Bradstreet JJ, Smith S, Baral M, Rossignol DA. Biomarker-guided interventions of clinically relevant conditions associated with autism spectrum disorders and attention deficit

hyperactivity disorder. Altern Med Rev. 2010; 15:15-32

de Theije CG, Wu J, da Silva SL, et al. Pathways underlying the gut-to-brainconnection in autism spectrum disorders as future targets for disease management. Eur J Pharmacol. 2011; 668:70-80

Dhillon S, Hellings JA, Butler MG. Genetics and mitochondrial abnormalities in autism spectrum disorders: a review. Curr Genomics. 2011; 12:322-32.

El-Baz F, Ahmed Ismael N , Nour El-Din S. Risk factors for autism: an Egyptian study. The Egyptian Journal of Medical Human Genetics. 2011; 12:31-8

Emedicine health, http://www.emedicine-health.com/autism/page3_em.htm#Autism Symptoms. (accessed 2012 April 26).

Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. Br J Psychiatry. 2009; 195:7-14

Geiera DA, Kern JK, Garver CR, et al. Biomarkers of environmental toxicity and susceptibility in autism. J Neurol Sci. 2009; 280:101-8

Geraghty M. Nutritional interventions and therapies in autism: a spectrum of what we know: Part 2, ICAN: Infant, Child, & Adolescent Nutrition. 2010; 2:120-33

Gerber JS, Offit PA. Vaccines and autism: a tale of shifting hypotheses. Clin Infect Dis. 2009; 48:456-61

Ghanizadeh A. c-Kit+ Cells Transplantation as a new treatment for autism, a novel hypothesis with important research and clinical implication. J Autism Dev Disord. 2011; 41:1591-2

Ghanizadeh A. Targeting neurotensin as a potential novel approach for the treatment of autism. J Neuroinflammation. 2010; 7: 58-9

Ghanizadeh A. Targeting of glycine site on NMDA receptor as a possible new strategy for autism treatment. Neurochem Res. 2011; 36: 922-23

Goines P, Van de Water J. The immune system's role in the biology of autism. Curr Opin Neurol. 2010; 23:111-7

Green JJ, Hollander E. Autism and oxytocin: new developments in translational approaches to therapeutics. Neurotherapeutics. 2010; 7: 250-7

Guastella AJ, Einfeld SL, Gray KM, et al. Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. Biol Psychiatry. 2010; 67:692-4

Gupta S, Samra D, Agrawal S. Adaptive and innate immune responses in autism: rationale for therapeutic use of intravenous immunoglobulin. J Clin Immunol. 2010; 30:90-6

Hoogduijn MJ, Popp F, Verbeek R, et al. The immunomodulatory properties of mesenchymal stem cells and their use for immunotherapy. Int Immunopharmacol. 2010; 10:1496-500

Huffman LC, Sutcliffe TL, Tanner IS, Feldman HM. Management of symptoms in children with autism spectrum disorders: a comprehensive review of pharmacologic and complementary alternative medicine treatments. J Dev Behav Pediatr. 2011; 32:56-68

Ichim TE, Solano F, Glenn E, et al. Stem cell therapy for autism. J Transl Med. 2007; 5:30-9

Johnson CP, Myers SM. Identification and evaluation of children with autism spectrum disorders. Pediatrics. 2007; 120:1183-215

Koenig K, Levine M. Psychotherapy for individuals with autism spectrum disorders. Contemporary Psychotherapy. 2011; 41:29-36

Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism, a review and integration of findings. Arch Pediatr Adolesc Med. 2007; 161:326-33

Landrigan PJ. What causes autism? Exploring the environmental contribution. Curr Opin Pediatr. 2010; 22:219-25.

Mayoclinic. Autism risk factors. http://www.mayoclinic.com/health/autism/DS00348/DSECTION=risk-factors. (accessed 2012 April 25).

Modi ME, Young LG. The oxytocin system in drug discovery for autism: animal models and novel therapeutic strategies. Horm Behav. 2012; 61:340-50

Momin EN, Mohyeldin A, Zaidi HA, et al.Mesenchymal stem cells: new approaches for the treatment of neurological diseases. Curr Stem Cell Res Ther. 2010; 5:326-44

National institute of neurological disorders and stroke. Autism fact sheet. http://www.ninds.nih.gov/disorders/autism/detail_autism.htm. (accessed 2012 April 27).

Panerai S, Zingale M, Trubia G, et al. Special education versus inclusive education: the role of the TEACCH program. J Autism Dev Disord. 2009; 39:874-82

Pring L, Ryder N, Crane L, Hermelin B. Creativity in savant artists with autism. Autism. 2012; 16:45-57

Pubmed health. Autism. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002494/. (accessed 2012 April 25).

Rapin I. Current concepts: autism. N Engl J Medicine. 1997; 337:97-104

Rapin I, Tuchman RF. Autism: definition, neurobiology, screening, diagnosis. Pediatr Clin North Am. 2008; 55:1129-46.

Ratajczak HV. Theoretical aspects of autism: causes-a review. J Immunotoxicol. 2011; 8: 68-79

Risi S, Lord C, Gotham K, et al. Combining information from multiple sources in the diagnosis of autism spectrum disorders. J Am Acad Child Adolesc Psychiatry. 2006; 45:1094- 103

Rossignol DA, Frye RE. A review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures. Mol Psychiatry. 2012; 17:389-401

Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. Mol Psychiatry. 2012; 17: 290-314

Sala M, Braida D, Lentini D, et al. Pharmacologic rescue of impaired cognitive flexibility, social Deficits, increased aggression, and seizure susceptibility in oxytocin receptor null mice: a neurobehavioral model of autism. Biol Psychiatry. 2011; 69: 875-82

Siniscalco D, Sapone A, Cirillo A, et al. Autism spectrum disorders: is mesenchymal stem cell personalized therapy the future? J Biomed Biotechnol. 2012; 2012:1-6

Treffert DA. The savant syndrome and autistic disorder. CNS Spectr. 1999; 4:57-60

Treffert DA. The savant syndrome: an extraordinary condition. A synopsis: past, present, future. Philos Trans R Soc Lond B Biol Sci. 2009; 364:1351-7

Villagonzalo KA, Dodd S, Dean O, et al. Oxidative pathways as a drug target for the treatment of autism. Expert Opin Ther Targets. 2010; 14:1301-10

Webmd. Autism symptoms. http://www.webmd.com/brain/autism/autism-symptoms. (accessed 2012 April 25).

Webmd. Autism - Treatment overview. http://www.webmd.com/brain/autism/autism-treatment-overview. (accessed 2012 April 26).

White JF. Intestinal Pathophysiology in Autism. Exp Biol Med (Maywood). 2003; 228:639-49

You Y, Wu B, Shen Y. A pilot study on the diagnostic performance of DMS-IV and DMS-V for Autism Spectrum Disorder. N A J Med Sci. 2011; 4:116-123