Blood Markers in Detection of Autism

https://doi.org/10.3991/ijes.v9i2.21283

Theodora Stavridou, Anna Maria Driga, Athanasios Drigas (✉)
Net Media Lab-Mind & Brain R&D,
N.C.S.R. 'Demokritos', Athens, Greece
dr@iit.demokritos.gr

Abstract—The current paper gives a brief description of the relationship of biomarkers with autistic spectrum disorder, we discuss autism, study the biomarkers which can be traced by medical tests, their association with the triggering of autistic behaviors, and finally we discuss how the regulation and balance of these biomarkers could reduce the autistic symptoms.

Keywords—Autism, biomarkers, enzymes, omega-3 fatty acids, folic acid, vitamin B1, probiotics oxidative stress, toxins, heavy metals, mercury, pesticides, maternal infections, mitochondrial dysfunction, gluten, neurodevelopment

1 Introduction

Autism is a lifelong neurodevelopmental disorder characterized by deficits in oral verbal communication, as well as the presence of stereotyped behaviors. According to researches and multi-year studies, scientists have concluded that biomarkers can show if a child has ASD.

Biomarkers are substances that are detected in the blood and urine. In children with autism biomarkers usually are at lower levels, such as antioxidant enzymes, omega-3 fatty acids, folic acid, vitamin B1 and probiotics. Another biomarker is oxidative stress, which is caused by environmental toxins and toxic substances, such as heavy metals, mercury, pesticides, maternal infections, as well as mitochondrial dysfunction, has been involved in the etiology of autism.

Other studies in children with autism have identified clear phenotypes (gastrointestinal problems, bacterial neurodevelopment, as well as excess gluten). Abnormalities in serotonin levels have yet to be observed.

From all these studies it was conducted that, in addition to heredity, an important role in the occurrence of autism plays exogenous factors, which if they disappear (oxidative stress, gluten) or if various substances such as omega-3, vitamin B1, folic acid are given, will there has been significant improvement in behavior.

2 Genomes and Chromosomes

Jianjun et al [2] report that analysis of genotype 333 in families with two affected individuals with autism, showed that, it is linked to chromosome 5X, 15 and 19. They also mention that autism disorders result from multiple allergic interactions, sensitive to environmental factors.

The methods used to diagnose autism, were a questionnaire by pediatricians (Diagnostic Interview, ADOS), brain imagining, urine and blood analysis, as well as psychological tests.

The results of several similar studies, were that chromosomes 5X, 15 and 19 are responsible for autism. [1], [2], [3], [4].

3 Serotonin

Autism is a childhood neurodevelopment disorder characterized by a weakening of social interactions and communication with appearance of behavioral stereotypes. According to Subhranghu and other teams, [5], [6], [7], [8] et al. many studies have shown an increase in blood serotonin (5-HT) levels in autistic individuals, but also of neuropsychiatric disorders. This proves abnormalities of serotonergic neurotransmission.

The methods used for the above investigations, were whole blood tests, urine tests, as well as positron emission tomography.

The result of these studies, [5], [6], [7], [8] is that except for genes, a significant role in the development of autism, also plays elevated blood serotonin levels.

4 Inflammations

Theocharis C Theocharides [9] et al. report that studies have shown different immunological abnormalities in children with autism. However, to find evidence of immune activation in the central nervous system in children with autism, inflammation markers were measured in the cerebrospinal fluid, such as quinolinic acid, neopterin, biopterin and levels of the inflammatory cytokine.

The methods were applied, were a quinolinic test in the cerebrospinal fluid by modification of gas chromatography.

The result of all of these measurements was that both quinolinic acid and neopterin, as well as increased cytokines, are sensitive inflammatory markers.

The conclusion was that reduced levels of neopterin [9], [10] were found in the cerebrospinal fluid, as well as quinolinic acid, but increased biopterin.

5 Fatty Acids

A human brain contains a high concentration of lipids that contribute to the synthesis of neuronal phospholipid membranes (PL). For its development, polyunsaturated fatty acids omega -3 and omega-6 are essential.

Stephen et al. [11] report that in various studies in children with autism, there is a lack of this supplement.

Besides, each of the autism scales, such as irritability, social withdrawal, stereotypes, inappropriate speech, and especially hyperactivity, showed improvement with the administration of fatty acids.

The methods used, were plasma testing of children with autism, using chromatographic methods to quantitatively measure many classes of lipids and fatty acids.

The conclusion drawn from these investigations [11], [12], [13] was that hyperactivity, was significantly reduced by the administration of omega-3 fatty acids.

6 Neurotrophins Neuropeptides

Autism spectrum disorder (ASD) characterized by social interaction disorders, verbal and non-verbal communication, as well as stereotyped behaviors.

According to Lisa A. Groen et al.[14] the increase in autism pushed for an intense effort to identify early biological markers. This research has shown that BDNF (brain-derived neurotrophic factor), which originates in the brain and is located in the entire central nervous system and in the peripheral blood, it is involved in the survival of neuromuscular nervous in the developing brain. BDNF is trophic for serotonergic neurons and serotonin levels are the most common in autism. A high concentration of NT-4 (neurotrophin) was also observed in people with autism. [14], [15].

The methods used were the use of ELISA technology, as well as the use of Luminex technology was increased levels of BDNF were found in the plasma of children in autism.

7 Oxidative Stress

Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders characterized by social deficits, as well as repetitive behaviors.

Both genetic predisposition as well as environmental toxins and toxic substances, such as heavy metals, mercury, pesticides, polychlorinated diphenyls as well as maternal infection, have been implicated in the etiology of autism. The impact of these environmental behaviors is associated with increased oxidative stress, [16], [17].

Oxidative stress causes molecular damage manifested by lipid peroxidation, DNA, and protein modification (3-NT). A 3-NT increase in the cerebellum has been observed in autism, Alzheimer's, and Parkinson's disease.

Oxidative stress can be detected by studying various markers in urine and erythrocytes, such as protein and polyunsaturated fatty acids (PUFA).

From all of these studies on erythrocytes membranes come to a conclusion that in causes of dyslexia, hyperactivity, and attention deficit, there is a reduced concentration of PUFA (ω3 –ω6).

8 Intestinal Flora

Autism syndrome is a complex neurobiological disorder characterized by impaired communication, as well as repetitive stereotyped behaviors.

Studies in people with autism have shown that these people suffer from gastrointestinal problems. This is mainly due to administration during the first years of life, which eliminate the beneficial bacteria and help the pathogenic microbes to fall in the intestinal flora. These microbes interact with the central nervous system and show ASD behavioral symptoms.

Maria Florentino et al [18] discovered that children with autism were found with small amounts of Prevotella polysaccharides (beneficial germ) in the gut, which have the key genes for the biosynthesis of vitamin B1, as well as fish oil supplementation and Coptoccocus.

The methods used were stool tests, digestion markers, fatty acids, PH, and the presence of blood. Gastrointestinal problems were assessed with a modified questionnaire.

The conclusion from these studies was that children with autism have more gastrointestinal problems due to taking antibiotics, reduced consumption of fish, fish oil, probiotics, and B1, [18], [19] , [20], [21].

9 Immune Reactions

Autism spectrum disorders (ASD) are complex childhood developmental disorders characterized by impairment in social interaction, deficits in oral and verbal communication, as well as in various studies in children with ASD clear phenotypes have been identified (regression and profile of biochemical and immunological markers, gastrointestinal problems, as well as bacterial overgrowth, increased severity of the syndrome, and the beneficial effect of nutritional blockade of gluten).

Studies [21], [22], observed that in children with autism, there is the presence of inflammation in the brain and increased plasma cytokine levels, such as interleukin (1α), -1β, IL-6, and IL-8. Other studies have also shown an increase in NK cells in children with autism.

One method used is ileocolonoscopy to assess mucosal inflammation in children with autism, as well as lymphocytes (PH of the peripheral blood of the mucosa showed significant immune regulation of the immune system.

These studies conclude that children with autism have brain inflammation, as well as gastrointestinal problems due to intestinal permeability. That’s why many children on a gluten- free diet have been shown behavioral stereotypes. [23].

10 Cytokines

Autism is a neurodevelopment disorder characterized by social deficits, impairment oral communication, as well as the presence of stereotyped behaviors.

People with ASD have increased neuroinflammation in brain tissues, imbalance in immunoglobulins, including plasma levels of Ig G4, decreased levels of IgG, and imbalance in cytokines/chemokines levels.

Cytokines and chemokines are proteins involved in regulating hematopoiesis of inflammation and the proliferation of immune cells. Besides, they play an important role in normal neurodevelopment.

Qusseny Zerbo et al. [23] and Japanese researchers reported that children with autism and mental retardation have higher BDNF (brain-derived neurotrophic factor) concentrations.

Other studies [24] have shown that there is an association between maternal infections and inflammation during pregnancy and ASD and could be achieved through a disturbance of balance levels of cytokines/chemokines.

Methods used in these studies were a plasma test and amniotic fluid in children with autism.

The conclusion drawn from these researchers was that children with ASD are more likely to have reduced levels of MCP- 1 and reduced levels of RANTES.

11 Biomarkers in General

Autism is a lifelong neurodevelopment disorder characterized by deficits in oral and verbal communication, as well as the presence of stereotyped behaviors.

Mr. Andre A.S Coldani et al. [25] in studies have reported that biomarkers in autism may reflect genetic and neurological changes or epigenetic processes that may be active at certain times.

Genetic biomarkers: As autism is one of the most well-known physical disorders, researches have been conducted on possible biomarkers. In these studies, the heredity of ASD was verified.

Epigenetic biomarkers: ASD epigenetic changes occur through tissue modification methylation, RWA color modulation, and silencing. Processes in the environmental impact of the X gene that affect gene expression metabolic processes such as oxidative stress, chronic brain inflammation, diabetes, mitochondrial function, hyperglycemia, methylation, immune function, and stress, the maternal and paternal immune system, toxic to the environment and diet.

The many promising biomarkers include those for mitochondrial function, oxidative stress, and immune function. Some children with ASD have a spectrum of mitochondrial function. 80% of patients with ASD may be acquired rather than inherited.

Oxidative stress is detected by studying the antioxidant enzymes in the blood, the peroxidation of fats, and the oxidation of proteins that are increased.

Examinations of biomarkers may lead to the treatment of metabolic abnormalities such as phenylketonuria, cerebral acid deficiency, and creatinine deficiency, as well as an excess of prionic acid.

12 Conclusion

In conclusion, according to researches on autistic people, scientists have concluded that autism, which is a neurodevelopmental disorder, is due to both heredity and environmental factors (oxidative stress, heavy metals, gluten etc.). Also, in the absence of omega-3 fatty acids, vitamin B1, folic acid, and serotonin we observe manifestations of autistic behaviors. Finally, studies approved that when regulation and balance of the Markers guide to a new homeostasis, there will be an improvement in the behavior of these individuals.

13 References

[1] Elizabeth Petit et al. X Chromosome and Infantile Autism, Biol. Psychiatry 1996; 40: 457-464

[2] Jianjun Liu et al. Columbia Genome Center and Departments of Psychiatry, Los Angeles. A Genomewide Screen for Autism Susceptibility Loci. Am. J. Hum. Genet. 69: 327-340, 2001

[3] Stephen J. Glatt et al. Ph.D, Blood –Based Gene Expression Signatures of Infants and Toddlers With Autism. Journal of the American Academy of Child & Adolescent Psychiatry Volume 51 Number 9: 934-944, September 2012 https://doi.org/10.1016/j.jaac.2012.07.007

[4] Anne Philippe et al. Genome-wide scan for autism susceptibility genes. Human Molecular Genetics, 1999 Oxford University Press, Vol. 8, No.5 805-812

[5] Stefano Gabriele et al. Unit of Child and Adolescent NeuroPsychiatry, Laboratory of Molecular Psychiatry and Neurogenetics. Blood serotonin levels in autism spectrum disorder: A systematic review and meta- analysis. European Neuropsychopharmology(2014) 24, 919- 929 www.elsevier.com/locate/euroneuro. https://doi.org/10.1016/j.euroneuro.2014.02.004

[6] Joseph Piven et al. Johns Hopkins University School of Medicine. Platelet Serotonin, A Possible Marker for Familial Autism. Journal of Autism and Developmental Disorders, Vol. 21, No. 1, 1991

[7] Alexander Kolevzon et al. Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA. Relationship between whole blood serotonin and repetitive behaviors in autism. Psychiatry Research (2010) 274-276 journal homepage: www.elsevier.com/locat/psychres. https://doi.org/10.1016/j.psychres.2009.02.008

[8] Subhrangshu Guhathakurta et al. Manovikas Biomedical Research and Diagnostic Centre, Manovikas Kendra, Rehabilation and Research Institute for the Handicapped, 482 Madudah, Plot 1-24, Sector-J Bypass, Kolkata, India. Analysis of serotonin receptor 2A gene (HTR2A): Association study with autism spectrum disorder in the Indian population and investigation of the gene expression in peripheral blood leukocytes. Neurochemistry International 55 (2009) 754-759 www.elsevier.com/locate/neuint https://doi.org/10.1016/j.neuint.2009.07.008

[9] Theocharis C Theocharides et al. Focal brain inflammation and autism. Journal of Neuroinflammation 2013, 10:46 http://www.jneuroinflammation.com/content/10/1/46
[10] Andrew W. Zimmerman, MD et al. Cerebrospinal Fluid and Serum Markers of Inflammation in Autism, Pediatric Neurology 2005 33:195-201
[11] Stephen Bent et al. A Pilot Randomized Controlled Trial of Omega-3 Fatty Acids for Autism Spectrum Disorder, J Autism Dev Disord (2011) 41: 545-554 https://doi.org/10.1007/s10803-010-1078-8
[12] Sarah A. Brigandi et al. Autistic Children Exhibit Decreased Levels of Essential Fatty Acids in Red Blood Cells, International Journal of Molecular Sciences 2015,16, 10061 - 10076. www.mdpi.com/journal/ijms. https://doi.org/10.3390/ijms160510061
[13] S. Vancassel et al. Plasma fatty acid levels in autistic children, Prostagladins, Leukotrienes and Essential Fatty Acids (2001) 65(1), 1-7 http://www.ideallibrary.com. https://doi.org/10.1054/plef.2001.0281
[14] Lisa A. Groen et al. Brain-Derived Neurotrophic Factor and Autism: Maternal and Infant Peripheral Blood Levels in the Early Markers (EMA) Study, Autism Research 1: 130-137, 2008. https://doi.org/10.1002/aur.14
[15] Kaoru Miyazaki et al. Serum neurotrophin concentrations in autism and mental retardation: a pilot study, Brain & Development 26 (2004) 292-295 www.elsevier.com/locate/braindev. https://doi.org/10.1016/s0387-7604(03)00168-2
[16] Elizabeth M. Sajdel –Sulkowska et al. Brain Region – Specific Changes in Oxidative Stress and Neurotrophin Levels in Autism Spectrum Disorders (ASD), Cerebellum (2011) 10:43-48. https://doi.org/10.1007/s12311-010-0223-4
[17] Alessandro Ghezzo et al. Oxidative Stress and Erythrocyte Membrane Alterations in Children with Autism: Correlation with Clinical Features, June 2013 vol.8, issue 6 /e66418, www.ploseone.org
[18] Maria Fiorentino et al. Blood –brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders, Molecular Autism (2016) 7:49
[19] James B Adams et al. Gastrointestinal flora and gastrointestinal status in children with autism- comparisons to typical children and correlation with autism severity, BMC Gastroenterology 2011, 11:22 http:/www.biomedcentral.com/ 1471-230X/11/22. https://doi.org/10.1186/1471-230x-11-22
[20] Dae -Wook Kang et al. Reduced Incidence of Prevotella and Other Fermenters in Intestinal Microflora of Autistic Children, July 2013, vol.8, issue 7, e68322. www.plosone.org
[21] Paul Ashwood et al. Immune activation of peripheral blood and mucosal CD3+ lymphocyte cytokines profiles in children with autism gastrointestinal symptoms, Journal of Neuroimmunology 173 (2006) 126-134. www. elsevier.com/locate/jneuroim. https://doi.org/10.1016/j.jneuroim.2005.12.007
[22] Paul Ashwood et al. In Search of Cellular Immunophenotypes in the Blood of Children with Autism, May 2011, vol.6, issue 5, e19299. www.ploseone.org
[23] Qusseny Zerbo et al. Neonatal cytokine and chemokines and risk of Autism Spectrum Disorder: The Early Markers for Autism (EMA) study: a case-control study, Journal Neuroinflammation 2014, 11:113. http:/www.jneuroinflammation.com/content/11/1/113. https://doi.org/10.1186/1742-2094-11-113
[24] Philip G. Nelson et al. National Institute of Child Health and Development. Selected neurotrophins, neuropeptides, and cytokines: developmental trajectory and concentrations in neonatal blood of children with autism or Down syndrome, International Journal of development Neuroscience 24 (2006) 73-80. https://doi.org/10.1016/j.ijdevneu.2005.10.003
[25] Andre A. S et al. Biomarkers in autism, August 2014, vol.5, article 100, 1 www.frontiersin.org

14 Authors

Theodora Stavridou, is with Institute of Informatics and Telecommunications - Net Media Lab & Mind-Brain R&D, Agia Paraskevi, 153 10, Athens, Greece (e-mail: dora_stavridou@yahoo.com).

Anna Maria Driga, is with N.C.S.R. "Demokritos", Institute of Informatics and Telecommunications, Net Media Lab, Agia Paraskevi, 153 10, Athens, Greece (e-mail:anna.maria.driga@gmail.com).

Athanasios Drigas, is a Research Director at N.C.S.R. 'Demokritos', Institute of Informatics and Telecommunications - Net Media Lab & Mind-Brain R&D, Agia Paraskevi, 153 10, Athens, Greece (e-mail: dr@iit.demokritos.gr).

Article submitted 2021-01-18. Resubmitted 2021-03-08. Final acceptance 2021-03-09. Final version published as submitted by the authors.