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Review Article

Biomarkers in autism spectrum disorder – A review

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ABSTRACT

Autism is a disorder that is increasing many folds in incidence and is now considered an epidemic. There are no objective ways to confirm the disorder. Diagnosis is formed subjectively, supported by the perceived behavior of the subject. Therapeutic interventions have better results when started early in life in autism spectrum disorder, yet diagnosis often remains delayed, partly because it mainly relied on identifying abnormal behaviors which will be delayed or not emerge until the disorder is well established. Even so, many promising areas of research have disclosed abnormal biological processes that are related to ASD. Biomarkers that are identified on children who are at risk during the pre-symptomatic period can assist with early diagnosis, confirm behavioral observations, stratify patients into subgroups, and predict therapeutic response. Knowledge of the numerous biomarkers of ASD is important as it can go a long way in the early diagnosis of the condition and some may predict response to specific treatments. Through this review, we intend to give an insight into various biomarkers of ASD that have to date been established for its diagnosis and intervention. It's likely that biomarkers should be combined with other parameters to be effective to identify ASD early and guide proper therapeutic interventions.

1. Introduction

Autism spectrum disorder (ASD) is a complex developmental condition that involves persistent challenges in, speech, social interaction, nonverbal communication, and restricted/repetitive behaviors.[1] The term autism was then renamed autism spectrum disorder in 2013 by the American Psychiatric Association.[2] It's now an umbrella term that covers the following conditions: Autistic disorder, Asperger's syndrome, Childhood disintegrative disorder, and Pervasive developmental disorder not otherwise specified. Even so, many promising areas of research have disclosed abnormal biological processes that are associated with ASD. Biomarkers were developed to estimate biological abnormalities precisely and are vital in the diagnosis and management.[3] It refers to the aberrances in neurological and biological function in individuals diagnosed with autism. It's the goal of biomarker research to spot the biological changes specific to autism, thereby allowing researchers to develop more objective diagnostic tests, moreover as with earlier identification and intervention.

Biomarkers are objective measures of pathophysiological, biological, or pharmacologic responses to remedial interventions. By the Biomarkers Definitions working group,[3] common applications of biomarkers include:

1. Helps in diagnosing a disease by identifying individuals with abnormal processes,
2. Classifying disease severity
3. Predicting prognosis
4. Monitoring the response to therapy

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However, the diagnostic methods and screening tools utilized for ASD are somewhat subjective and are difficult to assess in younger children. Biomarkers are going to be utilized in multiple aspects of clinics to oversee patients with ASD, including fostering early diagnosis and selective medical attention.[3] This review talks about the cropping biomarkers which may be implemented for better diagnosis and prompt treatment. Through this review, we hope that the reader will procure a finer understanding of the promising biomarkers that will be made use of in various treatment modalities for ASD. This will be an unlimited area, and this review isn't intended to be comprehensive.

2. Neuropathologies in Autism

Although a precise pathway of mechanisms directed towards pathogenesis and a longtime link to autism on the symptomatic level exists; there are however several important theories (neural connectivity, neural migration, excitatory-inhibitory neural activity, dendritic morphology, neuroimmune response; calcium signaling, and mirror neuron) which appear to elucidate how autism develops. It seems probable that autism 's neurodevelopmental defect is of a multi-domain origin (rather than one anomaly) and is hence distributed across numerous levels of study (genetic, immunopathogenic, etc.). Biochemical and pathologic signs of autism present very early in life: Newborns with increased neurotransmitters are shown to develop autism at a later age.[4] The neuropathology of autism has its origins within the prenatal development of the brain, with an ongoing organic process that continues into adult life.[5]

3. Prenatal Biomarkers

3.1. Pre-eclampsia

Pre-eclampsia may trigger aberrant neurodevelopment through placental, maternal, and fetal pathophysiologic mechanisms. Preeclampsia results from shallow placentation which will result in fetal hypoperfusion. Association between pre-eclampsia and ASD was offered when brain MRI of 7–10 years old children (5 boys and 5 girls), offspring of pre-eclamptic pregnancies, revealed enlarged brain regional volumes within the cerebellum, lobe, and brain stem, and right and left amygdalae. These offspring also displayed reduced cerebral vessel radii within the occipital and parietal lobes. Enlarged left and right amygdalae were described in ASD and lobe epilepsy.

3.2. Genetic

Most centers offer routine screening for genetic birth defects, most notably mental retardation, and other trisomy disorders. Since it's a posh disorder with the involvement of several variants, each contributing with a reduced risk to phenotype, the identification of susceptibility genes has been difficult. According to Freitag some chromosomic deletions in 2q37, 7q31, 22q11, and 22q13.3, also are important within the cytogenetic evaluation of autism. By contrast, in about 2 to 4 percent of people with ASD, rare gene mutations or chromosome abnormalities are thought to be the cause of the condition, often as a feature of syndromes that also involve additional signs and symptoms affecting various parts of the body. For example, mutations in the ADNP gene cause a disorder called ADNP syndrome. In addition to ASD and intellectual disability, this condition involves distinctive facial features and a wide variety of other signs and symptoms. ARID1B, ASH1L, CHD2, CHD8, DYRK1A, POGZ, SHANK3, and SYNGAP1 are some of the other genes**.** Some of the candidate genes of idiopathic autism related to brain metabolism are AVPR1a, DISC1, DYX1C1, ITGB3, SLC6A4, RELN, RPL10, and SHANK3.

4. Biomarkers in the Gastrointestinal System

Individuals with autism may have differences in their gastrointestinal (GI) system, such as problems digesting certain foods. These GI abnormalities may be indicative of a predisposition to developing autism. The common GI difficulties include diarrhea, constipation, gaseousness, bloating, abdominal pain, stool impaction, reflux, and belching. Autistic patients had elevated numbers of Paneth cells per crypt.[6] Porphyrins, derivatives of the heme synthesis pathway and measures of xenobiotic exposures, have been documented to be found at increased levels in the urine of autistic patients.[7] In addition, a calcitonin gene-related peptide was reported to be increased in the blood of autistic subjects.[4] Another study of urine from autistic patients documented increased levels of several peptides, e.g., Deltophin II, Dermorphin, and Desmorphin (opioid-like peptides), morphine modulating peptide, and Novel Autism Peptides I and III.[8]

In contrast, more recent studies have not found evidence of opioid peptides in the urine of autistic children or young adults.[9] It is possible that the cause of the opioids found in the older studies was no longer present in the individuals studied by Hunter et al. and Cass et al.

5. Immunologic Biomarkers

Autoimmune responses are increased in autism. Levels of antibodies directed against autologous cerebellar peptides, dipeptidyl peptidase IV, and/or gliadin were increased in the serum of autistic subjects.[10] Serum or plasma levels of other autoantibodies including those against glial filament and neurofilament proteins, and myelin basic protein were also increased. Connolly et al. (2006) documented increased autoantibody levels against BDNF, brain endothelial cells, and myelin basic protein in the sera of autistic children.[11]

Levels of immunoglobulin A have also been documented to be low, but those of cytokines interleukin (IL)-1β and IL-6 were elevated in the mononuclear blood cell cultures of autistic patients. Other studies have also reported elevated levels of tumor necrosis factor (TNF)-α, soluble IL-2, and soluble CD8, as well as IL-12 and interferon (IFN)-γ. Vargas et al. (2005) studied the brain tissues from deceased patients with autism for concentrations of cytokines.[12] Eighteen cytokines were quantitated in the middle frontal gyrus, anterior cingulated gyrus, and/or cerebellum, and in the cerebrospinal fluid (CSF) of autistic individuals. The most prominent being macrophage chemoattractant protein (MCP)-1 and tumor growth factor-β1.[13]

The cerebellum has been the most focus of neuroinflammation in autism.[11] The foremost prominent cytokines within the brain of autistic patients were C4B complement protein was found to be deficient in the blood of autistic patients. The C4B protein is important within the activation of the classical complement pathway that ends up in lysis. C4B is taken into account as a regulatory protein and covalently binds to the surface of target cells. within the absence of C4B, the system is partially compromised.[11] Other abnormal immune parameters in autism reported were lymphocyte subsets, with helper (CD4+) T-lymphocytes, and natural killer cells documented as deficient. Inversely correlated with symptoms of autism was the helper: suppressor (CD4:CD8) ratio.[12] Autistic individuals had fewer lymphocytes with bound IL-2 on their surface following mitogenic stimulation. Alternately, DR+ activated T-lymphocytes were increased within the blood of autistic patients in contrast to normal IL-2 receptors on lymphocytes, suggesting incomplete activation of the cells, often seen in an autoimmune disorder.[12]

6. Neurologic Biomarker

To date, the strongest evidence implicates systems involved with glutamate, gamma-aminobutyric acid (GABA), and serotonin systems (with melatonin as a major effector) in autism, with weaker evidence for changes in catecholaminergic, peptidergic, and cholinergic systems. Moreno et al. (1992) documented that glutamate was increased in the plasma of autistic individuals.[13] An abnormality in the GABA system in autism was first documented by Blatt et al. (2001), who found that GABA receptor systems are significantly reduced in high-binding regions. The suppressed GABA inhibition may contribute to the pathophysiology of autism.[14]

Platelet hyperserotonemia is mostly considered the foremost robust and well-replicated biological finding in autism.[15] Serotonin plays a key role in behaviors and processes, including sleep, mood, arousal, aggression, impulsivity, and affiliation. within the embryo, serotonin acts as a protein and regulator of neuronal development.[16] Serotonin could be a precursor of melatonin. Melatonin is decreased in the urine, saliva, and blood of autistic patients in autism, the amount of melatonin is below normal, and a biological time in its production isn't displayed.

Testosterone is increased within the serum of autistic individuals, and there's an impression of testosterone on melatonin secretion. Norepinephrine and epinephrine are decreased in the urine of autistic individuals. Blood levels of adrenocorticotropin hormone (ACTH) were increased in autistic subjects in contrast, cortisol was decreased.[17] However, cortisol was increased in autistic children in anticipation of re-exposure to a perceived stressor. A slower elevation of cortisol after ACTH stimulation was documented for autistic individuals when put next to normal individuals. Biopterin and neopterin were increased in the urine of 3–5-year-old autistic children. Neopterin is related to the activation of cell-mediated immunity and it accompanies the immune activation of macrophages; both IFNγ and TNFα cause increased amounts of neopterin to be produced. thanks to a rise in BH4 biosynthesis, levels of biopterin were also found to be increased in autistic patients. Neurotrophins have multiple functions during peripheral and central systema nervosum development, like regulating the expansion, development, survival, and repair of the system.[18]

7. Toxicologic Biomarkers

The liver shows reduced levels of glutathione (GSH) within the plasma of autistic subjects in contrast to those of oxidized glutathione (GSSG) that were increased. GSH plays a significant role in methylation, a process that's intimately involved in detoxification.[19]The methylation cycle of autistic individuals is aberrant in each of its steps, with the expression of most key markers being under those found up to the mark children. These include methionine, S-adenosylhomocysteine (SAM), homocysteine, cystathionine, cysteine, and total GSH. In contrast, greater values were found for S-adenosylhomocysteine (SAH), adenosine, and oxidized glutathione (GSSG). SAM and SAH are metabolites of the Met cycle. Met is the only real substrate of methionine adenosyltransferase (MAT) for the synthesis of SAM, while SAM is the universal methyl donor for various methyl-transfer reactions, including the methylation of DNA, and RNA, proteins, phospholipids, and neurotransmitters, all told living organisms.[19] Sulfate within the gut is an element of the body's first line of defense against toxicants, neutralizing various substances before they will be absorbed. The metabolism of cysteine is the largest source of sulfate within the body.[20] Children with autism have low plasma sulfate levels. Abnormal sulfation has the strong potential of causing or contributing to several abnormalities commonly seen in autism, including leaky gut syndrome, detoxification abnormalities, and neurotransmitter dysfunction.[21] The

abnormal sulfation may well be caused by the decreased amount of phenylsulphotransferase in autistic children, which decreases the metabolism of phenolic foods known to form abnormal behavior in autistic children.

8. Ubiquitous Biomarkers

8.1. Amino acids

Amino acids documented to be decreased in the blood of autistic subjects include aminoalkanoic acid, glutamine, aminoalkanoic acid, and Gamma-aminobutyric acid (GABA). Evans et al. reported significantly lower urinary levels of essential amino acids for both untreated autistic children (aged 5–15 years) and people treated for digestive function and nutritional uptake.[22] Arnold et al. reported that plasma from children (< 5 years old) with autism had more essential organic compound deficiencies (including the neurotransmitter precursors tyrosine and tryptophan) that were in line with poor protein nutrition.[23] In contrast, Aldred et al.reported that 4–16 year old autistic subjects had elevated plasma levels of aminoalkanoic acid, phenylalanine, asparagines, tyrosine, alanine, and lysine, concurrent with reduced levels of glutamine.[24] Autistic individuals also exhibited decreases in the plasma levels of phospholipid fatty acids and pyruvate within the serum. Carnitine has also been determined to be decreased in the serum of autistic patients. In contrast, the amount of alanine (α-amino propionic acid; one amongst the amino acids occurring widely in proteins), together with ammonia, is increased in the serum of autistic patients.[25]

8.2. Cyclic adenosine 3′5′monophosphate (cAMP)

cAMP could be a second messenger involved in many processes including mnemonic processing and anxiety memory deficits and anxiety are noted within the phenotype of fragile X (FX), the foremost common heritable reason behind subnormality and autism.[26] In contrast, plasma levels of cAMP are elevated in medicated and unmedicated autistic children (those without FX) relative to levels in controls. The opiate theory of autism proposes that autistic individuals have a hyperactive opiate system. The cAMP produced from opioids could also be a useful biomarker to differentiate between FX and autism.[26] Additionally, the cAMP cascade could also be a viable therapeutic target for both FX and autism.

9. Metabolic Biomarkers

Examples of metabolic disorders that can lead to an autistic-like presentation include phenylketonuria (PKU), disorders of purine metabolism, biotinidase deficiency, cerebral folate deficiency, creatine deficiency, and excess propionic acid (which is produced by Clostridium).[27] The authors identified four main mechanisms that have been increasingly studied during the past decade: immunologic/inflammation, oxidative stress, environmental toxicants, and mitochondrial abnormalities. The brain is highly vulnerable to oxidative stress, particularly in children during the early part of development. As environmental events and metabolic imbalances affect oxidative stress and methylation, they also can affect the expression of genes.[28]

10. Blood Biomarkers

Based on the understanding of the etiology of ASD, many blood-based biomarkers have been investigated, particularly neurotransmitters, cytokines, markers of mitochondrial dysfunction, markers of oxidative stress, and impaired methylation.[29]

10.1. Oxidative stress markers

Oxidative stress could even be detected by studying antioxidant status, antioxidant enzymes, lipid peroxidation, and protein/DNA oxidation, all of which are elevated in children with autism. Different subgroups of kids with ASD have different redox abnormalities, which could arise from various sources.[30] Measuring reduced glutathione, oxidized glutathione, or the ratio of reduced glutathione to oxidized glutathione helps determine the patient ‘s oxidation status. In many patients with ASD, the ratio of reduced glutathione to oxidized glutathione is decreased, indicating a poor oxidation status. The enzyme antioxidant has been used as a marker and is typically reduced.[31] Other markers for glutathione inadequacy include alpha hydroxybutyrate, pyroglutamate, and sulfate, which might be assessed in an organic appraisal. Lipid peroxidation refers to the oxidative degradation of cell membranes. there’s an enormous correlation between the severity of autism and urinary lipid peroxidation products, which are increased in patients with ASD.[32]

10.2. Plasma F2t-isoprostanes

(F2-IsoPs) are the foremost sensitive indicator of redox dysfunction and are considered by some to be the gold standard measure of oxidative stress. They’re increased in patients with ASD and are even higher when in the midst of gastrointestinal dysfunction. F2t-isoprostanes (F2-IsoPs) are measured within the urine further.[32]

10.3. Urinary 8-hydroxydeoxyguanosine (Urinary 8-OHdG)

This is a biomarker for oxidative damage to DNA which has been seen to increase in children with ASD. Decreased levels of major antioxidant serum proteins transferrin (iron-binding protein) and ceruloplasmin (copper-binding protein) have been observed in patients with ASD.[32] The levels of reduction in these proteins correlate with loss

of previously acquired language although there are mixed reviews of the significance of this.[32]

10.4. Plasma 3-chlortyrosine (3CT)

This is a measure of reactive nitrogen species and myeloperoxidase activity, which is a longtime biomarker of chronic inflammatory response. Plasma 3CT levels reportedly increased with age for those with ASD and mitochondrial dysfunction but not for those with ASD without mitochondrial dysfunction.[32]

10.5. 3-Nitrotyrosine (3NT)

A plasma measure of chronic immune activation may be a biomarker of oxidative protein damage and neuron death. This measure correlates with several measures of cognitive function, development, and behavior for subjects with ASD and mitochondrial dysfunction but not for subjects with ASD without a mitochondrial dysfunction.[32]

10.6. Mitochondrial dysfunction markers

Mitochondrial dysfunction is marked by impaired energy production. Some children with ASD are reported to possess a spectrum of mitochondrial dysfunction of differing severity. Mitochondrial dysfunction, presumably an early event in neurodegeneration, is one of the more common dysfunctions found in autism and is more common than in typical controls. there's no reliable biomarker to spot all cases of mitochondrial dysfunction. Markers of mitochondrial dysfunction include lactate, pyruvate, and lactate-to-pyruvate ratio, carnitine (free and total), quantitative plasma amino acids, ubiquinone, ammonia, CD, AST, ALT, CO2 glucose, and creatine kinase (CK).[32] Many studies of ASD report elevations in lactate and pyruvate, others report a decrease in carnitine, while others report abnormal alanine in ASD patients or elevations in aspartate aminotransferase and serum CK. Increases in lactate don't seem to be specific and should only occur during illness, after exercise, or struggling during a blood draw.[30]

11. Social Biomarkers in Autism Spectrum Disorder

Social interaction deficits are evident in many psychiatric conditions specifically in autism spectrum disorder (ASD), but hard to assess objectively. Difficulties within the encoding of emotions are a defining characteristic of autism spectrum disorder. Similarly, differences in signaling emotions are characteristic of ASD. Such clinical measures include evaluating the patient's facial expressivity and gaze behavior by a trained clinician following a consistent protocol.[33] However, interrater-variability may account for inconsistencies regarding diagnostic accuracy. Especially individuals with ASD and average or above-average intelligence are often diagnosed later in life, as they develop strategies to catch abreast of their deficits, which has been spoken of as camouflaging. Atypical gaze patterns are furthermore characteristic of ASD—especially the avoidance of direct eye contact. Moreover, ASD involves aberrant voice intonation, especially in naturalistic settings. The SIT aims at reliably capturing those social biomarkers, which may aid earlier diagnosis likewise as monitoring the course of the disorder and treatment outcome. Individuals with ASD expressed less social smiling and fewer mimicry of positive facial expressions than HC individuals.[33]

12. Maternal Antibody and ASD

Autoimmune diseases primarily affect women and are more prevalent in mothers of youngsters with neurodevelopmental disorders. for instance, mothers of youngsters with autism spectrum disorder (ASD) are significantly more likely to possess an autoimmune disorder than women of neurotypically developing children. Moreover, they're four to 5 times more likely to harbor brain-reactive antibodies than unselected women of childbearing age.[34] Brain-reactive antibodies have the potential to change brain development in utero leading to damage that may be persistent and result in neurodevelopmental and neuropsychiatric disorders within the offspring. it's been proposed that AD-related impaired B lymphocyte tolerance in women can result in the assembly of those antibodies. Indeed, ADS is more prevalent in mothers of children with neurodevelopmental and neuropsychiatric disorders including ASD. An etiological role for maternal antibodies in ASD is plausible thanks to the gestational transfer of maternal IgG during pregnancy where maternal IgG is detected in the circulatory system as early as 13 weeks of gestation in humans. By 30 weeks of gestation, levels within the fetal compartment reach approximately 50% of circulating levels within the mother, with levels at birth exceeding maternal IgG levels. The developing barrier is actively changing during fetal neurodevelopment and is permissive to IgG molecules during this era.[34]

13. Anti-Ganglioside M1 Auto-Antibodies

Serum levels of anti-ganglioside M1 antibodies were increased in many autistic children. Also, their levels had significant positive correlations with the degree of the severity of autism. Thus, autism is also, in part, one amongst the pediatric autoimmune neuropsychiatric disorders. the foremost important clue for the possible role of autoimmunity in autism is the presence of brain-specific auto-antibodies in many autistic children.[35] Also, there's a powerful association between autism and

also the major histocompatibility complex for the null allele of C4B within the class III region. This ends up in low production of C4B protein resulting in repeated infections which play a very important role within the development of autoimmunity. additionally, in some autistic children, there's an imbalance of T-helper (Th)1/Th2 subsets toward Th2, which are answerable for the allergic response and also the production of antibodies. The role of immunotherapy in autistic patients who have increased serum levels of anti-ganglioside M1 antibodies should even be studied.[35]

14. Serum Antinuclear Antibodies

Some autistic children have an imbalance of T-helper (Th)1/Th2 subsets toward Th2, which are responsible for allergic response and the production of autoantibodies. Brain-specific auto-antibodies were detected in the sera of many autistic children.

15. Cytokine Dysregulation in Autism Spectrum Disorders

Cytokines are mediators of immunological activity which has significant interactions with the system. They participate in normal neural development and performance, and inappropriate activity incorporates a spread neurological implication. It is, therefore, possible that cytokine dysregulation contributes to neural dysfunction in ASD. Further, cytokine profiles change fiercely in the face of infection, disease, and toxic exposures. Imbalances in cytokines may represent a response to environmental contributors to ASD.[36]

16. Minor Physical Anomalies in Autism Spectrum Disorder

Minor Physical Anomalies (MPAs) are subtle abnormalities of the top, face, and limbs, without significant cosmetic or functional impact to the individual. They're assumed to represent markers of deviant morphogenesis during the primary or early trimester of pregnancy and to own ectodermal embryonic origins in common with the developing brain.[37] Genetic factors and prenatal events, like maternal bleeding with subsequent fetal hypoxia, gestational diabetes, medication use, or toxemia, may contribute to MPAs. In ASD, MPAs are suggested to be the external markers for atypical brain development, and excessive MPAs are found when put next to neurotypically developing children. In a study, interorbital and interlens distances were measured using an MRI scan and showed that hypotelorism (i.e., short interorbital length) is also present in an exceeding subgroup of people with autism and IQ within the conventional lower range.[38] Macrocephaly in autism was first noted by Kanner (1943), the primary person to explain the disorder. Recent studies indicate that autism is related to enlarged total cerebral volume, abnormal electroencephalograms, increased substantia alba, and decreased nervous tissue.[37] Abnormalities within the medial lobe, cerebellum, and amygdala are observed. Head circumference in children younger than age 6 could be a good index of total brain volume. Head circumference in children with autism is usually smaller than normal or normal at birth, yet increases faster than normal at around 4 months old.[39] Approximately 60% of kids with autism show this atypical trajectory to an extreme degree, while only 6% of typically developing children show this atypical trajectory. Ref As noted during a study by, at ages 2–4 years, 90% of boys with autism had larger than normal brain volumes, and 37% met the standards for developmental macrocephaly. Ref variety of studies has reported that 2D:4D (length of the second finger divided by the length of the fourth finger) is smaller in autism spectrum disorder (ASD) or ASD-affected individuals than in unaffected controls.[38] MPAs reported in ASD are observed across multiple areas of the body, including the pinnacle, hands, and feet. Rodier et al. studied the frequency of individual MPAs in ASD and located that posterior rotation of the ear was more common in children with autism compared to the overall population, furthermore as compared in children with developmental delays.[38]

17. Conclusion

The lack of one identified cause for autism leaves much to be discovered within the field. Although there are many potential biomarkers for predicting the chance of developing ASD before birth, many of those biomarkers haven't been systematically studied to get estimations of the associated risk of developing ASD after birth. Several diagnostic biomarkers are promising but just like the pre-symptomatic biomarkers, the studies remain very preliminary. Thus, to point to autism, which may be a spectrum of disorders, single markers are going to be inadequate. Considering the large array of biomarkers in ASD, a knowledge of the identical is important for a pediatric dentist, to be ready to recognize the disease at the earliest, to assist the patient get early intervention.

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None.

19. Conflict of Interest

The authors declare no conflict of interest.

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