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ROLE OF BODY FLUIDS IN ETIOLOGY, PATHOGENESIS & DETECTION OF AUTISM SPECTRUM DISORDERS (ASD'S)

Medicine

Dr Suraj Bhola	BDS
Dr Dhiraj Bhambhani	MBBS
Dr Suresh Bhambhani	MD, Medicine, Professor, Chirayu Medical College and Hospital, Bhopal
Dr Janisar Javed	MD Psychiatry, Consultant Psychiatrist, Bansal Hospital, Sagar
Anusha Gopala-krishnan Iyer	
Ramani Raman	

ABSTRACT

In order to aid in diagnosis, offer precise prognostic data, and track illness development, current research on neurological diseases is concentrated on developing novel disease biomarkers. With improvements in detection and quantification techniques in genomics, proteomics, and metabolomics, saliva has become a reliable source of samples for the identification of disease biomarkers. Saliva collection is a painless, non-invasive operation that does not need for special training and has no adverse effects on the patient. In this article, we review the research on salivary biomarkers and consider the accuracy of these indicators in the diagnosis and follow-up of neurodegenerative and neuropsychiatric illnesses, such as autism. According to research alpha-synuclein, salivary nitrate levels , microelements like zinc , copper , serum and salivary IgG4 , salivary IgA and micro-RNA profiles have a high level of consistency and validity as disease biomarkers.

KEYWORDS

Biomarkers, Neurodegenerative , Neuropsychiatric, Alpha-synuclein , Micro-RNA

INTRODUCTION

Autism is defined as a disorder of neural development which is characterized by an impaired social interaction , communication and by restricted and repetitive behavior, and in which symptoms begin before 7 years of age. An Austrian-American psychiatrist and physician, Dr. Leo Kanner first described autism in 1943. Donald Triplett , an American male who was the first person to be diagnosed with autism. Scientists speculate that autism is caused by an unknown genetically determined brain abnormality that occurs early in development [1] .The heritability of autism has been estimated to be as high as 90% [2].Noto et al. (2014) reported that 1 out of 88 children aged 8 years will develop an Autism Spectrum Disorder (ASD) , with males more at risk than females. Blumberg et al. (2013) showed that the prevalence of Autism Spectrum Disorder (ASD) had risen 75 % from 2007 to 2012 in the United States [3] . It has also been reported that in twenty first century the rate of autism cases per 1000 children grew significantly in the United States.

The first report of autism in Indian scientific literature may have been made in 1944 by a Pediatrician from Vienna named A. Ronald, he provided an overview of the identification, causes, characteristics, and treatment of what he labelled "abnormal children." In Indian literature, the term "autism" first emerged in 1959[4].

According to research conducted in Asian nations, approximately 1.7–2 million people in India are thought to be affected by Autism Spectrum Disorder (ASD) [5]. Currently in India, it is estimated that around 18 million people have Autism, Prevalence rate is approximately 1 in 500 or 0.20% or more than 2,160,000 people in India [6] and incidence rate is approximately 1 in 90,666 or 11,914 people [6]. The number of reported cases of autism increased significantly in 1990s and early 2000s. This increase can possibly be due to greater public and professional awareness, changes in diagnostic practices, referral patterns, availability of services and perhaps unidentified environmental risk factors may also be implicated.

Autism Spectrum Disorder (ASD) affects approximately 1–2% of the population, and the average male to female ratio is 4–5:1 globally [7]. According to some studies [8] Synaptic synthesis and organization is affected by autism in the brain but its exact mechanism is poorly understood, Advanced parental age especially of fathers also plays a dominant role in the occurrence of Autism Spectrum Disorders (ASD's) as the aged fathers cause a greater risk than older mothers possibly due to increase in mutation in older sperms. It is also believed that race, ethnicity, and socioeconomic conditions do not affect the occurrence of autism.

Exact pathophysiology of autism is not known, but some studies [9] reveals that autism is primarily inherited, although its genetics due to complexity remains unclear. Environmental factors that have been claimed to be the cause of autism, or may be important in future research, such as certain foods, infectious disease, heavy metals, solvents, diesel exhaust, phthalates and phenols used in plastic products, pesticides, brominated flame retardants, alcohol, smoking, illicit drugs, vaccines and prenatal stress.

Various Programmes Running On Autism -

1. Globally [10,11,12] –

- Global Autism Public Health Program (GAPH)
- Global Autism Interactive Network (GAIN)
- Global Outreach Autism Learning Services (GOALS)

2. In India [13]-

- The National Trust for Welfare of Persons with Autism , Cerebral Palsy , Mental Retardation and Multiple Disabilities.
- Samarth Scheme
- GHARAUNDA (Group Home And Rehabilitation Activities for Disabled Adults)
- Niramaya (Health Insurance Scheme)
- VIKAAS Day Care

Pathogenesis

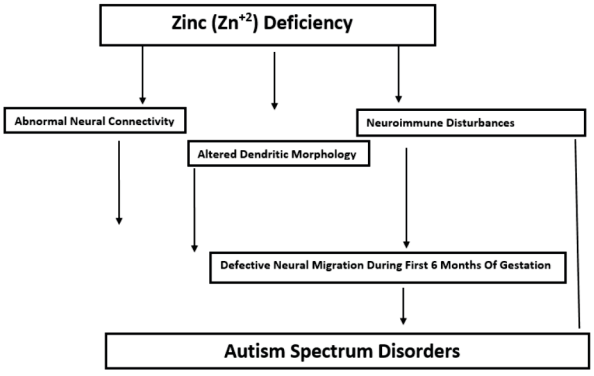
In the central nervous system (CNS) , bioelements are vital. Deficiency of essential minerals and trace elements are recognised to contribute to a number of health issues, including the development of Autism Spectrum Disorders (ASD's).

Zinc is one of the essential trace element, an important antioxidant. It is crucial for the proper functioning of immune system, protein and DNA synthesis, wound healing, and cell division, throughout pregnancy, childhood, and adolescence, zinc promotes healthy growth and development. Neuropsychological changes such as emotional instability, anger, and sadness can occur in people with severe zinc insufficiency. Lack of zinc also affects proper neurotransmission, brain development, connection and cognitive functions of an individual. Lack of zinc is a significant environmental stressor that has the

potential to be identified as a contributing component in the pathogenesis of Autism Spectrum Disorder (ASD), regardless of whether it is caused by internal or external (environmental) factors .

What Is The Role Of Early Diagnosis Of Autism Spectrum Disorders (ASD) In Children?

Early diagnosis of any disease leads to start of early treatment of that particular disease which results in good prognosis. According to Centers for Disease Control (CDC) Although people with autism cannot "outgrow" the disorder, it is treatable, and studies have shown that early detection and intervention have a considerable positive impact on outcomes[14]. An early diagnosis enables parents to take action and start assisting their child, as opposed to observing symptoms and wondering that something is wrong with them. Parents can start following the recommended treatment to help their child progress throughout his or her developmental phases under the direction of specialists and organizations like Alternative Behavior Strategies (ABS), laying the groundwork for noticeably improved outcomes [15].



Role Of Salivary & Serum Biomarkers in Early Diagnosis Of Autism:

1) Estimation Of Salivary Levels Of Alpha-Synuclein Monomer & Oligomer in Children with Autism Spectrum Disorder : A Prospect for an Early Diagnosis

Alpha, beta, and gamma synuclein subclasses make up the small (14kDa), naturally unfolded human synuclein protein family. The central nervous system (CNS) and presynaptic nerve endings are rich in alpha and beta types, whereas the peripheral nervous system (PNS) is primarily the site of gamma type expression. Lewy bodies are pathological proteinaceous filamentous structures found in many neurodegenerative diseases, like Parkinson's diseases, Autism Spectrum Disorders (ASD's) and alpha-synuclein emerges as a major component of these bodies. Biological fluids like blood, sputum, saliva and cerebrospinal fluid (CSF) can all be found to contain a-synuclein (a-syn) . Children with ASD also have changes in plasma a-synuclein levels, which suggests synaptic dysfunctions in these circumstances. Alpha-synuclein is present in the cells as alpha-synuclein-monomer in physiological circumstances but in certain neurodegenerative diseases like ASD , Parkinsonism, it abnormally aggregates into alpha-synuclein-oligomers which further gets converted into amyloid fibrils which acts as a precursor for the formation of Lewy bodies.

In some studies [16] Salivary samples were collected from the children (four to eight years of age group) both healthy and affected by Autism Spectrum Disorder (ASD). As a result concluded from the above mentioned study, children with Autism Spectrum Disorder (ASD) have low amounts of alpha-synuclein monomer and oligomer in their saliva.

2) Salivary Nitrate Levels & Autism:

The central nervous system (CNS) and peripheral nervous system (PNS) both uses nitric oxide (NO) as one of their primary signaling molecules. Nitric Oxide (NO) works as a signaling molecule at low concentrations, in nervous system nitric oxide (NO) is important in neurogenesis and neurodevelopment. Abnormal NO signaling contributes to the formation of numerous neurodevelopmental, neurobehavioral, and neurodegenerative disorders.

The involvement of Nitric Oxide (NO) in the development of Autism Spectrum Disorder (ASD) was first reported by Amal et al . According to a study [17] conducted Salivary nitrite levels in the ASD group were substantially greater than those in the normally developing group, Children with ASD showed a positive connection between saliva NO_2^- and serum NO_3^-, whereas the normally developing group did not. As a result salivary & serum both Nitrates levels are higher in Autism Spectrum Disorder (ASD) children but these levels did not correlate with the severity of disease.

3) Salivary Micro RNA Levels in Autistic Patients:

The expression of genes is regulated post-transcriptionally by little RNA molecules called microRNAs (miRNAs), which are 21–25 nucleotide length. MiRNAs are crucial for the growth of the central nervous system, hence miRNA dysregulation is linked to the altered behaviour and thinking processes seen in a variety of illnesses, including ASD.In children suspected of having developmental disorders (DD), such as ASD, miRNAs can be employed as biomarkers [18].

Children with ASD have "altered" salivary microRNA levels that are related to the severity of ASD behaviours. Salivary microRNA collection is non-invasive and has a mediocre accuracy in determining ASD-status.

4) Zinc, Copper & Severity Of Autism

Neuropsychological alterations such as emotional instability, irritability, and sadness can occur in people with severe Zinc insufficiency[19], cognitive functions are also hampered by zinc insufficiency (Black, 1998) [20]. According to a study by Takeda et al. 2006a zinc is also required for synaptic neurotransmission as an intracellular signal factor[20].

Lakshmi Priya and Geetha in 2011 stated that the effects of copper (Cu) poisoning on the brain are significant. Copper at toxic levels can have mild to severe effects on the mind, depending on the degree of toxicity and the individual's vulnerability [20]. According to Madsen and Gitlin (2007), excessive Cu exposure may cause neurotoxic side effects such as sadness, irritability, fear, anxiousness, learning and behavioural impairments, and perhaps Alzheimer's disease [20].

According to a study of Deinum et al. 2004, Rahman et al. 2009 , Dopamine – hydroxylase (DBH) requires the cofactor copper to function [20]. This enzyme that produces neurotransmitters changes dopamine into norepinephrine. Lake et al. in 1977 stated that Autistic people have been reported to have higher norepinephrine levels[20].

Children with an Autism Spectrum Disorder (ASD) are more likely to have Zn insufficiency and Cu poisoning [20]. When compared to a control group and other study groups, a significant difference in Zinc levels was discovered in the hair and nails of children in the low functioning autism group in a study by Lakshmi Priya and Geetha (2011) [20]. In comparison to children with moderate and high functioning autism, those in the low functioning autism group had higher concentrations of copper in both hair and nail samples. This finding might imply that the severity of a child's autism increases with increasing Cu toxicity[20].

Zinc to Copper Ratio:

A high serum Copper concentration is almost always correlated with a low plasma Zn concentration. Published research of Van Weyenbergh et al. 2004, Faber et al. 2009 shows that children and adults typically have a Zn to Cu ratio close to 1:1.) [20]. According to certain theories (Aschner et al. 2006, Faber et al. 2009), Mercury (Hg) toxicity may be a significant factor in children with ASD having metallothionein dysfunction, which may be reflected in the Zn/Cu [20].

In 2009, Faber and colleagues conducted a retrospective study of plasma Zn, serum Cu, and Zn/Cu ratio on children with autistic disorder, as a result of this study conducted , the average Zn/Cu ratio was lower than normal Zn/Cu ratio [20].

5) Serum & Salivary IgG_4 Levels Correlation With Autism:

The findings reveal that the elevated levels of IgG_4 in serum among autistic children, which had a positive correlation with the salivary IgG_4. This is suggestive of the usefulness of salivary IgG_4 levels for early detection of ASD, and confirms that saliva can be a noninvasive assessment tool for health monitoring among children with ASD.

Salivary IgA levels in Autism Spectrum Disorder (ASD), Some studies also reveals that salivary IgA levels are also reduced in the Autistic children and is of significant diagnostic value [21].

6) Sphingosine1-phosphate And Docosahexaenoic Acid (DHA) As

Potential Serum Biomarkers In Autism :

According to some studies , sphingosine 1-phosphate and docosahexaenoic acid were specifically linked to autism , there levels are high in serum of autistic patients [22].

Biomarkers Demonstrated in Cerebro-Spinal Fluid (CSF) Of Autistic Patients:-

New research over the past five years has shown that Cerebrospinal fluid (CSF) also plays a crucial role in brain growth and function during pregnancy and throughout life. In a study Cerebrospinal Fluid (CSF) samples had been taken during the medical treatment of 0- to 3-month-old febrile infants and then stored at -70 °C , and Oxytocin and Arginine Vasopressin (AVP) levels were measured . Autism Spectrum Disorder (ASD) cases had considerably lower neonatal Cerebrospinal Fluid (CSF) Arginine Vasopressin (AVP) concentrations compared to that of healthy infants. These preliminary results imply that a neurochemical marker of Autism Spectrum Disorder (ASD) may be present at a very young age.

CONCLUSION

The first report of autism in Indian scientific literature may have been made in 1944 by a Pediatrician from Vienna named A. Ronald. Autism Spectrum Disorder (ASD) affects approximately 1-2% of population , and the average male to female ratio is 4-5:1 globally. Exact mechanism of autistic disorders are poorly understood, advanced parental age especially of fathers also plays a dominant role in the occurrence of Autism Spectrum Disorder (ASD) . Race, ethnicity and socioeconomic conditions do not affect the occurrence of autism. Exact pathophysiology of autism is also not clear.

In the Central Nervous System (CNS), Zinc and copper are the essential trace elements. Children with Autism Spectrum Disorders (ASD's) tend to be more susceptible to Zn insufficiency, Cu toxicity, low Zn/Cu ratios, and dysfunctional metallothionein (MT) systems. Children with Autism Spectrum Disorder (ASD) show lower amounts of alpha-synuclein monomer and oligomer, which set them apart from children with other degenerative brain illnesses. Abnormal Nitric Oxide (NO) signaling also contributes to development of Autism Spectrum Disorder (ASD). The dysregulation of microRNA's is linked to altered behavior and thinking process seen in variety of illness , including Autism Spectrum Disorder (ASD).The elevated levels of IgG_4 in serum among autistic children has a positive correlation with the salivary IgG_4. Salivary IgA levels are also reduced in children with Autism Spectrum Disorder (ASD). Sphingosine -1 phosphate and docosahexaenoic acid are specifically linked to autism , their levels are high in serum of autistic patients. New research over the past five years has shown that Cerebrospinal Fluid (CSF) also plays a crucial role in brain growth and function during pregnancy and throughout life. Autism Spectrum Disorder (ASD) cases have considerably lower neonatal Cerebrospinal Fluid (CSF) Arginine Vasopressin (AVP) concentrations compared to that of healthy infants.

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