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Review Article

Medicinal Effect of Zinc For The Cure of Autism Spectrum Disorder

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ABSTRACT

Autism Spectrum Disorder (ASD) is a cognitive deficiency and repetitive-sensory functionality and behavior. Due to uncertain diagnosis on the base of biomarker, it could be diagnosed on the base of clinical presentation for example irritable behavior towards social circle, and tendency of being isolate themselves along with speech problems and diminished interest in daily activities of life. ASD prevalence has been noticed high in male than females. There are about 350,000 autistic patients in Pakistan. Early screening and social awareness are the most controlled way to overcome the severity of disorder. Among the risk factor of maternal pathology, pollution and use of drugs, diet lacked mainly in zinc and other micro nutrients during phase of pregnancy play important role to affect the fetus brain function and structure. Autistic child being deficient in zinc nutrient affects their dietary choices in a way that their taste buds and olfactory sense don't function well in food selection that is highly depend on zinc function in body result in malnutrition in the ASD children. This behavior shows a strong relation between high zinc diet and control of Autism symptoms. Ketogenic diet, gluten and casein free diets might be beneficial in autism according to some studies. Zinc, being the utmost rich trace metal in brain and is very crucial for neurodevelopment and pathological process of autism. SHANK proteins are principal scaffolding proteins and are vital for synthesis and function of synapses. The mutation in shank genes result in impairment of nerve transmission in autism patients. Zinc level is associated with optimal functioning of shank proteins and its deficiency may lead to inactivation of these proteins. In this review, we have discussed the regulation of SHANK 3 and its activation which are zinc dependent and result the elevated synaptic transmission.

INTRODUCTION

the early stage of the childhood. It causes the barrier in child normal social behavior and interaction, speech problems and decline interest in games and activities. The symptoms vary from person to person that the reason it is known as term spectrum of disorder. Mover over the autism children face compromised functionality in sensory and integration in daily and social matter of life [1]. However, the severity of affected child is from mild to severe from each other but basically it is diagnosed on the base of abnormal behavior and interaction in social life and having problem in communication skills. These children usually do stammer speech, poor eye contact, deficit in social interest and blank response to their name, exigent and impulsive behavior. Autistic kids have attention seeking behavior like, poor relation with peers and parents, habit of repeating words loudly, piling objects, keenly observed behavior towards moving object [2]. The onset of autism is before 3 years of age and mostly it occurs in males than females [3]. Due to the uncertainty of biochemical test, it can be diagnosed on the base of clinical signs and symptoms. However, prominently lack of cope with social behavior and cognitive skills, in children from different race, cultural and social background has been noticed worldly including Pakistan. There are many hereditary and ecological factors that researcher believed could be the reason of autism in child such as presence of any pathology, pollution, pregnancy complexity, maternal health issues, drugs has mostly been observed in western world [4] countries like Pakistan, health care system budget is only 1 percent annually that use for health and in this minimum budget it is almost impossible to cope with the autism patient and their parents , so providing social awareness and education to

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parents could be the possible way to reduced and control the worst situation in the autism spectrum children [5]. The first line of defense for the parents who are concerned for the development and improvement of their autistic kids are medical health professional of physician and pediatricians. Most of the time, complain that parents of ASD children recorded is that their children have tendency to isolate and refrain themselves socially. Health care and medical professional need to be more awarded and educate themselves about autism so that they can help parents to diagnose and make intervention plan on early stage for autistic children [1]. The American Academy of Pediatrics has advocated using proper screening tools for all young children to detect autism during primary care visit. It is important to do screening for autism at initial stage of childhood so that the possible risk can be detected whether parents and pediatrician are concerned of children developmental skills or not. The advantages that the early screening can give is that it can help to improve children reduced skills and cognitive development associated with autism at initial stage and can control further detriment if the child is at a risk or with ASD [6]. Early assessments, intervention, and monitoring has showed very positive results in improving skills and minimized the cognitive loss in ASD children. But unfortunately, services like this are unavailable in Pakistan. In rural areas, due to lack of awareness and facilities about autism, people kept ASD patients enchained and locked. Autistic children have a high IQ, and their learning styles differ from those of typical children. Many of them have a strong desire to master computer, music, mechanical, and painting abilities. In order to teach children in all of these talents, they need be taught at a young age. According to a study, the probable reasons of autism in a person might be due to impaired (GI) tract functionality. Researchers have discovered a link between abnormal GI tract function and autism. Another major aspect is maternal health and the low maternal mortality rate [7].

Relationship between Diet and Autism: The importance of smell in food intake, by selection of food to satisfaction and acceptance, cannot be overstated eating is a multifaceted mechanism that is affected by three major factors such as the food consumer (food choices and feelings), the object (food types and its stuffs), and the circumstances (bodily and societal). It is possible to learn to eat healthy. Sensorimotor, social, and psychological skills are necessary for the development of children's eating habits. The method can be frustrating at times: More than 80% of autistic children and 13–50% of children who are neurotypically developed suffer from eating disorders [8]. Selectivity, in fact, seems to be the most common issue that children with ASD confront [9], while the word "diet choosiness" has been interpreted in a range of means in research of ASD adolescents, here is various arrangement that limits the amount of appropriate food. The main aim of food education is to expand the number of foods that children accept in order to fulfil their basic dietary requirements. During childhood and puberty, this opening grows stronger and widespread. Many intrinsic and extrinsic influences, such as maternal activity or physical routes, affect children's adoption of new foods. One of the most possible bases that improved food choices and food intake in children with autism is due to their improved sensory functioning. In particular, olfactory changes in ASD children can jeopardize food acceptance and dangerously reduce diet variety [10]. Kids with Autism Spectrum Disease (ASD)have challenges using their visual, tactile, and auditory systems to choose novel foods. In a case study conducted on children with ASD, the role of neuron that helps in sense of smell, plays role in the eating behavior construction, as well as the amount and sense of diet neophobia in this culture, were discussed [11]. Food choosiness is more widespread in kids with ASDs than in normally developing kids, according to another study, and a reduced food selection can be linked to nutritional deficiencies [12]. Study demonstrates that when a food is viewed visually, children with ASD have more trouble liking it than children without ASD. Our results also show that time control is an important consideration to remember during the food selection process. They also offer novel approaches to assess and comprehend food phobia in children with ASD. Unusual sensory processing was observed in more kids with ASD as compared to kids without ASD. Unusual verbal sensual feeling caused children with ASD to refuse more nutrients and eat less root vegetable than children with normal verbal sensual feeling. The results indicate that using oral sensory integration techniques in attempts to report diet choosiness in children with ASD can be beneficial [13]. Picky consuming, diet choosiness, and diet denial are all typical habits in autistic children but some kids eat as little as five foods. Picky eating habits may be a product of ritualistic or projecting practices, as well as repeated behavior patterns. Others assume picky eating is caused by a child's aversion by modified, rigid, sensory sensitivities, as well as involuntary evidence of bad eating time behaviors, GI problems, and oral motor delays [14].

Zinc and Autism: Zinc deficiency has been related to a number of health issues. Patients of neurological conditions, in particular, often have zinc deficiency Low serum zinc levels have been related to Autism Spectrum Disorders, Mood Disorders such as depression, Attention Deficit Hyperactivity Disorder (ADHD), Schizophrenia and Spinocerebellar Ataxia Type 2 (SCA2), for example [15]. In

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another study, zinc deficiency was inflicted on rats during pregnancy and lactation. A Morris water maze was used to assess learning at 56 days of age. Prenatal zinc deficient animals took longer to reach the secret platform and swam longer distances as a result [16]. Rhesus monkey offspring with a significant zinc deficit placed on a breastfeeding woman in her third trimester exhibit learning disability later in life, as demonstrated by difficulties recalling previously mastered tasks requiring visual discrimination and difficulties learning new tasks. When taken together, prenatal zinc deficiency can cause long-term deviations in synapse structure or neuronal connectivity, resulting in decreased learning and memory capacity later in life, depending on the mission [17].Given the multifaceted impact of zinc on gut production and morphology in offspring, maternal zinc status may be a significant factor. Multiple causes affect and are affected by zinc status, and there is a potential interdependence with fetal and early life trauma, immune system defects, compromised GI functions, and zinc deficiency. Systemic inflammatory activities and prenatal stress have also been related to an elevated risk of ASD. We present a novel model based on these findings that shows how changes in maternal zinc status can have a pathological effect on offspring, resulting in brain function impairments later in life. Deficiency of zinc during birth can be very corporate, with expected 17 percent of the world's inhabitants vulnerable. In a specific to men and women sample, only a few female distinctions were discovered. Assumed that ASD mouse models often exhibit similar behavioral disruptions as mentioned here, we came to the conclusion that prenatal zinc deficiency is a problem in animals, even if they do not have a clear genetic susceptibility to ASD, already exhibit ASD-like conduct [18]. This means that giving Zn to autistic children, particularly those with Zn deficiency, may be an essential part of a therapy plan. Since these two suggestion essentials are rivals in role and compulsory for living cells, it is serious to way and track the ideals during Zn treatment, both Cu and Zn can be used together. The GABAergic structure can be active in ASDs, affording to studies, and Zn and Cu may play a major role in this system [19].

Mechanism of Zinc in ASD: Mostly the clinical symptoms of autism appear within first 3 years' life which is also duration of synthesis and processing of synaptic connections. Thus, a number of genes linked to autism areinvolved in the coding of synaptic proteins like SHANK family of protein. There is also a strong relation between synaptic debt and environmental factors associated with autism such as deficiency of zinc and inflammation in prenatal period during crucial time of development of brain. It emphasizes synapses as a main hub of environmental and genetics association [20].

SHANK Proteins: SHANK proteins are principal scaffolding proteins. They are situated at the region of excitative synapses where their role is critical for optimum synthesis and function of synapses. In vivo, the genes involved in coding of these proteins areShank1, Shank 2 and Shank 3 etc. [21]. These shank proteins also called synapse-associated protein 2 (proline-rich) (ProSAP2) perform a remarkable function in the synthesis, fostering, preservation and also in optimal synaptic transference and resilience. So, genetic mutations may lead to drastic imbalance of synapses are progressively related to neurological disorders like autism (ASD)[22]. As autistic patients have SHANK genes mutations so for better comprehension, the mechanism of autism and for making its therapeutic plans animal studies are used. In ASD patients, mutations in the three genes of shank occur [23].

Zinc Deficiency: The inadequate amount of zinc is linked with exhibition of neuropsychiatric problems like depression, behavior change, cognitive impairment and low potential for learning. Zinc is primarily concealed in glutamatergic neurons by commonly performing a role of inhibitory regulator at the receptor for glutamate NMDA (N-Methyl-D-Aspartate) in the limbic system. Zinc has high tolerance level with very low adverse effects. The typical method to take zinc is orally through dietary supplements and different compounds like zinc sulfate, zinc oxide etc. having a diverse range of absorptive capacity and tolerance [24]. The deficiency of trace mineral zinc has presently been related as causative factor for autism taking as environmental determinant. Thus, its deficiency is taken into account for autistic patients [25]. About seventeen percent (17%) population across the globe is at risk of deficiency of zinc remarkably during gestation and also in modern communities [26]. In autistic children, the zinc deficiency rate is fifty percent (50%). Hence, zinc is very crucial in neurodevelopment and pathological process of autism [27].

Zinc and SHANK Proteins:

Age	Male	Female	Pregnancy	Lactation
0 to 6 mo	2mg	2mg		
7 to 12 mo	3mg	3mg		
1 to 3 yrs	3mg	3mg		
4 to 8 yrs	5mg	5mg		
9 to 13 yrs	8mg	8mg		
14 to 18 yrs	11mg	9mg	12mg	13mg
19+ yrs	11mg	8mg	11mg	12mg

Table 1: Recommended Dietary Allowances (RDAs) for Zinc [28]

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Study Design	Sample size	Study Model	Methods	Results
Case Control study [28]	A total of 72 ASD patients were linked to 234 non-ASD panels	Human Based	Serum zinc stages were linked amongclasses,andage,sex, supplement use, and diet were all taken into account.	ASD group zinc lacking 86% of the timeNon-ASD control group only 24%Between the ASD and non-ASD clusters, there was a 175 mol /l variance in serum zinc levels (P0001).
Case Control study [29]	30 kids with ASD of both sexes, reaching in age from 3 to 8 years	Human Based	The effects of Zn supplementation on ASD children were studied for 3 months. Every daily dose of Zn was determined.Metallothione in 1 is a type of metallothionein that is found (MT-1A) and the harshness of autism. The Childhood Autism Rating Scale (CARS) is a tool for assessing autism in children.	The impact of Zn on the gene appearance of MT1-A was Investigated. Following zinc supplementation, they found an improvement in cognitive-motor presentation, an increase in serum metallothionein meditation, and reduction in circulating s erum copper levels. The hereditary appearance of MT-1 was complex after Zn cure in the ASD patients'
Case Control study [30]	Paternities of kids with ASD aged 2–18 years	Human Based	The control group healthy kids who went to the pediatrician for regular blood testing. Vitamin supplement-taking children were removed from both the ASD and control categories. Vitamin A and Zinc ranks were measured in the samples using standardized laboratory procedures.	Both groups had typical zinc and vitamin A levels. The mean (SD) zinc levels in the two groups were similar ASD versus control. (p value = 0.86). The ASD group had a higher mean vitamin A level versus, (p value=0.03), but this was possibly due to age.
Case Control study [31]	Mutant mice	Animal Based	CTTNBP2-regulated synaptic proteins share three c haracteristics: A connection to autism, the NMDAR-SHANK pathway, and zinc-related guideline.	Zinc supplementation increases CTTNBP2-regulated protein synaptic expression. Zinc supplementation and NMDAR coagonist D-Cyclo-serine boost the social activities of Cttnbp2-deficient MICE
Case Control study [32]	Mice with a prenatal zinc deficiency (PZD)	Animal Based	Two groups after one week of acclimation: One was given a zinc-deficient diet (4 ppm zinc, SSNIFF diets) and purified, demineralized water to drink.Other was served regular work shop nutrition (35 ppm zinc). Females from the control and zinc deficient groups were reproduced after 5 weeks and kept on their particular diets throughout pregnancy.	On the mRNA and protein levels, PZD mice have no marker gene expression differs by hemisphere. PZD mice have a higher striatal length. But no difference in overall brain volume. Furthermore, behavioral patterns linked to striatal lateralization have been changed, as Dopamine receptor 1 (DR1) expression is lateralized in the cortex stratum of PZD mice.
Case Control Study [33]	28 children with ASD and 28 safe controls	Human Based	Mass spectrometry with an inductively coupled plasma-sector region was used to measure Zn and Cu levels in whole blood. The values of whole blood Cu and Zn in both the control and the ASD groups followed a Gaussian distribution.	In contrast to controls, the ASD children had 10 percent and 12 out of a hundred lower levels of whole blood Zn and Zn/Cu ratio, separately.Cu levels in whole blood did not vary expressively. However, the Cu/Zn ratio in ASD children was 15 percent higher (p=0.008) than in control offspring.
Case Control Study [34]	Contestants were strained from four diverse trainings pleasing place in three altered countries	Human Based	Teeth and supporting data were collected from 25 ASD patients and 25 gender-matched controls who were enrolled in the study in ALSPAC. Additional replication analysis with ASD-diagnosed individuals (n =10) and their unaffected siblings (n = 8) at an autism clinic in New York, USA. The additional replication analysis was conducted with ASD-diagnosed individuals (n =10) andtheir unaffected siblings (n = 8).	Zinc-copper rhythmicity was interrupted in ASD belongings in all liberated study sets and in the pooled investigation. The cycle period was shorter consistency was cheap and complexity was reduced in ASD cases linked to controls. These results imply that different zinc-copper rhythmicity occurs prior to the onset of ASD, and that measureable biological measures of metal rhythmicity decide ASD cases from panels.

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Case Control Study [35]	Shank3ex13-16-/- mice	Animal Based	The animals were offered either a regular zinc diet (30 ppm) or a zinc supplementation diet (150 ppm). Away from the zinc stages, the two egg white-based rodent nourishments were equal. On either diet, there were no negative effects on animal health or development. At 9–10 weeks of age, males and females were subjected to behavioral, electrophysiological, and imaging tests.	Supplementation prohibited ASD-related dull and worry behaviors, as well as shortages in social originality gratitude. Zinc supplementation amplified the enrolment of zinc delicate SHANK2 to synapses, reduced synaptic programme precisely through N-methyl-D-aspartate (NMDA)-type glutamate receptors, inverted the reduced decline of NMDA receptor (NMDAR)-mediated flows, and sealed long term potentiation (LTP) at cortico-striatal synapses.
Case Control Study [36]	71 patients in total 31 kids with ASD, 29 kids with ADHD,11 kids with ASD with comorbid ADHD (ASD-C) and hyperactive sub type	Human Based	Lead levels were suggestively upper in children with ASD aged 5 or less when related to controls, and they were also expressively complex in males with ASD when related to females (P = 0.001). ASD-C, ADHD, P=0.026), and ASD (9.64 percent, P =0.046) had minor blood manganese levels.	Lead levels were suggestively upper in children with ASD aged 5 or less when related to controls, and they were also expressively complex in males with ASD when related to females (P = 0.001). ASD-C, ADHD, P=0.026), and ASD (9.64 percent, P =0.046) had minor blood manganese levels.

Table 2: Summary of ASD Literature

CONCLUSION

Autism Spectrum Disorder is a disorder having distinct features of lack of social interaction, communication problems, repetitive behaviors etc. Multiple factor like genetic and environmental factors play a remarkable role in its etiology, Autistic children also face difficulties in their food selection due to sensory abnormalities. Zinc deficiency, particularly during prenatal age may have a profound effect to trigger autistic behavior. Shank proteins are important for normal synaptic transmission pathway. Increased zinc level has resulted in amelioration of autistic behavior, cognitive functions by activating the SHANK proteins thereby enhancing synaptic transmission. It has been supported by various animal studies. But further human clinical trials are imperative in order to verify the effectiveness of zinc and its dosage in autism. Nevertheless, zinc might be used as an adjunctive therapy to alleviate the symptoms associated with autism spectrum disorder. This review article will be fruitful for exploring the management of autism.

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