J Neurology Neuromedicine
www.jneurology.com
Journal of Neurology & Neuromedicine

Mini Review Open Access

Zinc Status in Hair Samples and Common Neurodevelopmental Disorders

Torsak Tippairote[1], Dunyaporn Trachootham[2]*
[1]BBH Hospital, Bangkok, Thailand
[2]Institute of Nutrition, Mahidol University, Nakhon Pathom, Thailand

Article Info

Article Notes
Received: September 09, 2017
Accepted: December 18, 2017

***Correspondence:**
Dr. Dunyaporn Trachootham, Institute of Nutrition, Mahidol University, Salaya, Phutthamonthon, Nakhon Pathom, 73170, Thailand; Telephone: 66-2-800-2380 ext. 326, Email: dunyaporn.tra@mahidol.ac.th, dif.dunyaporn@gmail.com

Keywords
Zinc
ASD
ADHD
Hair
Neurodevelopmental disorders
Children

ABSTRACT

Zinc status is an important modifiable factor in Attention Deficit and Hyperactive Disorders (ADHD) and Autistic Spectrum Disorders (ASD), the two most common neurodevelopmental disorders. Many studies reported low serum or plasma zinc level in children with these conditions. While hair zinc level can be obtained non-invasively in young children, the reports of the hair zinc levels in ASD and ADHD children were varied. ASD children were reported to have lower than or indifferent level of hair zinc from that of healthy children. In ADHD children, hair zinc levels were reported as either lower or higher than their healthy control groups. Many factors interplayed and affected measurement of hair zinc level. Until more standardized method has been established, currently the zinc level in hair samples may be used as screening or supporting evidence. Other functional zinc markers such as serum zinc concentrations, dietary zinc intakes, and percentage of stunting rate, are still needed to assess the zinc status in susceptible children.

Introduction

Prevalence of neurodevelopmental disorders, particularly ADHD and ASD, were increasing in the last two decades[1-3]. Many studies reported numerous factors, including non-modifiable factors, such as genetic predispositions, pre-, peri-, or postnatal events, and many modifiable factors, such as the nutritional and environmental factors that were accounted for pathogenesis and pathophysiology of these disorders[4-6]. Among those nutritional factors, zinc status in various tissue samples was frequently reported to be associated with ADHD and ASD children. A number of studies further supported the role of zinc supplement as the possible safe and important treatment in ASD and ADHD[7,8]. Analysis of zinc level in children's hair was done via non-invasive procedure and was preferably used to assess zinc status in many settings[9]. We here reviewed the current knowledge on hair zinc status in ADHD and ASD children.

Physiologic role of zinc in neurodevelopment

Undeniable roles of zinc in healthy brain development are well established. The unique zinc-containing molecules, known as several classes of Zinc finger proteins (ZFP), are responsible for the DNA-binding ability of many transcription factors. Thus, zinc indirectly regulates various gene expressions. While most of central nervous system (CNS) zinc are tightly bound to proteins such as transcription factors, enzymes, metallothionein, approximately 10% of zinc is freely localized in presynaptic vesicles of glutamatergic or GABA containing neurons[10-12]. These free zinc help in modulating a variety of postsynaptic receptors,

affecting neuronal signal transduction for moods, memory, cognition and attention[11,13-16]. The role of CNS zinc affects brain and neuron formation, remodeling and functions throughout the life span. During brain developmental processes, starting from the stage of neuron proliferation, axon and dendrite growth, synapse formation, pruning (selective elimination of unused synapse for development of learning and memory) and function to differentiation, zinc always plays its key supporting roles in various processes such as DNA synthesis, cell division, and modulation of apoptosis, oxidative stress and synapse functions[11,17]. Even in adult brain, these zinc involvements still persist and significantly affect an important variety of brain functions[15].

Possible roles of zinc in neurodevelopmental disorders

Studies in cell, animal and human models supported the crucial roles of zinc in healthy neurodevelopmental process. Inadequacy of zinc during neuronal differentiation stages decreased cell survival and altered synaptogenesis and synapse pruning. These process occur through different pathways such as DNA replication, transcriptional control, mRNA translation, apoptosis and microtubule stability[15,18-20]. Studies using animal models demonstrated that during critical brain development period, functional zinc level was tightly regulated by zinc transporters and buffering proteins[18,21].

In later neurodevelopmental stage, behavioral changes which were related to dopaminergic pathway genes expression, were shown to be associated with ZFP gene variants[22]. Abnormal behaviors and hippocampal developmental disorders were demonstrated in ZFP521 mutant mice[23]. Study of zinc deprivation in rhesus monkeys showed changes in attention and behaviors[24]. Human with zinc deficiency may show impairment in concentration and delay in cognitive development[25,26]. A recent study reported low hair Zn/Cu ratio in children with Phelan McDermid Syndrome (PMDS), a genetic disorder characterized by features of Autism spectrum disorders and deletion in SHANK3 (SH3 and multiple ankyrin repeat domains 3) genes. Mechanistic studies in cell culture model revealed that the observed Zn deficiency was likely due to decreased expression of Zn uptake transporters[27]. Besides attention and cognitive deficits, several studies using animal depression model showed that zinc-deficient diets could induce quantitative and qualitative changes in phospholipid-protein balance, and up-regulation of N-methyl-D-aspartate receptor (NMDAR) in hippocampus and prefrontal cortex[28-30].

Hair Zinc status in ASD and ADHD children

Many reports showed lower serum or plasma zinc level in ASD and ADHD than that of healthy children[31-33]. However, the association between zinc status in hair samples and ASD or ADHD risk were somewhat inconclusive. While most of reports showed lower hair zinc levels in ASD children than healthy controls, some reports showed no differences. For examples, a roentgen-fluorescence spectrometry study from Georgia and an atomic absorption spectrophotometry (AA) study from India showed significantly lower zinc in hair of ASD children than that of their matched controls[34,35]. Another ICP-MS study in Kingdom of Saudi Arabia (KSA) also reported lower hair zinc levels in ASD children than their control groups[36]. In contrast to these findings, recent inductively coupled plasma mass spectrometry (ICP-MS) study from Russia reported no difference, with average levels at 124.6 to 113.3 μg/g, of hair zinc level in ASD children, to their age-matched controls in concordance to the report of AA study from KSA in 2005[37,38]. A Meta-analysis of 12 studies from 1978 to 2012 also reported no differences in hair zinc level between their study groups[39]. Based on existing information, there were no reports of significantly higher hair zinc level in ASD than healthy children.

In ADHD children, a recent Egyptian ICP-MS study reported lower hair zinc level in 20 ADHD children as compared to their cut-off value at 108.9 μg/g, and to their healthy controls[31]. In contrast, a Polish AA study reported higher hair zinc level in ADHD than healthy children[40]. Our recent Thai ICP-MS study also reported higher hair Zn/Cu and Zn/P ratios in 45 newly diagnosed ADHD children than their healthy controls. The average hair zinc levels in this study were 92.9 and 85.4 μg/g in ADHD and healthy children, respectively. Interestingly, the higher hair zinc level was associated with higher number of inattention, hyperactivity and total ADHD symptoms[41].

Reports of hair zinc status in these common neurodevelopmental disorders were apparently swung to both possible conflicting ends, of particularly in ADHD children. These indicated the dynamic association between hair zinc status and these common neurodevelopmental disorders. Further studies are required to elucidate factors contributing to these observations. Furthermore, zinc is environmentally ubiquitous. It is possible that some, but not all reported results of analyses of zinc in hair were obtained with inadequately clean sample preparation technique[42]. Zinc also has ICP-MS analytical interferences[42]. It is possible that some groups are less adept at exploiting instrument capabilities for the effective elimination of interferences. The fact that zinc has analytical interferences and is environmentally ubiquitous might be possible additional explanations for the conflicting results reported by different groups.

Factors affecting hair zinc status in ASD and ADHD children

Mineral deposition into hair samples are different from other tissues. Unlike minerals in blood, hair minerals have

no reported roles in any physiologic functions. Instead it may preferably be viewed as excretory or wasting minerals[43]. External incorporation of minerals into hair samples is possible and probably affected the reported hair mineral levels. However, proper hair sample collection procedure can minimize such possibility[42]. Moreover, diverse analytical methods and different laboratory standards and settings may create variations in detected levels. Currently, there are still no universal standard and references in hair mineral levels[42-45]. Without proper regional references or control groups, it is then premature to determine the deficiency or excess state of minerals merely from hair level.

Genetic predisposition of individual affected zinc status in hair samples. For example, a patient with ASD related mutation in SHANK3 showed re-emerging of low Zn shortly after discontinuation of zinc supplementation[27]. This evidence implied that in susceptible individuals regular diet may not be sufficient to maintain functional zinc level and the level of measured serum/plasma or hair zinc level may greatly vary and be rapidly changed on different state of mineral exposure.

Maternal factors such as cigarette smoking may contribute to zinc status in human offspring. A study of maternal and neonatal scalp hair revealed that cigarette smoking by mothers was associated with lower zinc but higher cadmium and lead in hair of their neonates[46]. A study in 1,967 infants (0-3 years old) with ASD showed 43.5 and 52.5 % Zn deficiency in male and female infants, respectively[47]. Since development of nervous system starts from pregnancy and continues after birth, further studies of maternal factors affecting zinc status in ASD and ADHD children are worthwhile.

Regional and individual dietary pattern may affect the zinc status in hair samples [36, 41]. In fact, a study in ASD children participating in the Autism Treatment Network, USA utilized prospective 3-day food records found that ASD children aged 4 to 8 years consumed significantly less mineral Zn than that of the recommended amount[48]. Furthermore, another study found significant correlation between calcium intake and hair zinc status in Polish infants[49]. More studies should be performed to investigate the relationship between dietary intake and hair Zn status in ASD and ADHD children. In addition, interaction with other minerals may have also interfered with hair zinc status. In fact, a multi-element study in hair samples reported that zinc level was positively associated with calcium, phosphorus, and magnesium, while negatively associated with arsenic, aluminum, iron and molybdenum[41]. Zn concentration in blood stream is controlled by metallothionein – the metal-binding protein. Displacement of zinc from metallothionein by cadmium may lead to release of zinc into hair samples[50]. In fact, elevated blood level of cadmium concomitantly with lower blood level of zinc and elevated urine level of zinc were shown in many patients with tobacco-related diseases[51]. Moreover, diverse analytical methods and different laboratory standards and settings may create variations in the detected level in hair samples[42,45].

Zinc status and neurodevelopmental disorders in adults

Cumulative evidences support a crucial role of zinc on neurogenesis in both developmental and adult stages[15]. However, there were limited evidences of zinc status in adults suffering from neurodevelopmental disorders. Repletion of zinc was shown to ameliorate depressive behaviors in mouse models[28]. Degree of symptoms in patients with major unipolar depression were decreased when being treated with combination of zinc supplementation and anti-depressant drugs in a double-blind, placebo controlled study[52]. Even if the treatments are started in adulthood, reversing of maladaptive biochemical state can result in significant functional improvement in neurodevelopmental disorders despite irreversible neuroanatomical pathologies[53]. When zinc deficiency was confirmed, zinc repletion may be beneficial to adults with these neurodevelopmental disorders.

Conclusion

Disturbance of zinc homeostasis may contribute to clinical symptoms of ASD and ADHD as shown by hair zinc level changes in ASD and ADHD children from different mentioned studies. However, the correlation of hair zinc status and neurodevelopmental disorders seems to be more complicated than just either high or low measured level. Many internal and external factors seem to play roles in this dynamic interaction and warranted further studies.

In the meantime, low hair zinc level may be used as supporting evidences of zinc status in ASD and ADHD children. However, normal or high hair zinc level, particularly in ADHD children, do not entirely exclude the possibility of functional zinc inadequacy. Other functional zinc deficiency markers, such as low serum zinc concentrations, low dietary zinc intakes, and percentage of stunting rate in children, were needed to confirm the possibility of zinc deficiency state[54]. Zinc supplementation will be the beneficial option if there are convincing evidences of deficiency state[7,8,55].

Acknowledgement

The author thanks Mr.Eugene Kilayco, a professional English editor for proof-reading and editing the manuscript. Parts of the work described in this paper was supported by The National Research Council of Thailand (FY2016; Thesis Grant for Master Degree Student).

References

1. Gurney JG, Fritz MS, Ness KK, et al. Analysis of prevalence trends of autism spectrum disorder in Minnesota. Archives of pediatrics & adolescent medicine. 2003; 157(7): 622-7.
2. Charman T. The prevalence of autism spectrum disorders. Recent evidence and future challenges. European child & adolescent psychiatry. 2002; 11(6): 249-56.
3. Brown RT, Freeman WS, Perrin JM, et al. Prevalence and assessment of attention-deficit/hyperactivity disorder in primary care settings. Pediatrics. 2001; 107(3): E43.
4. Rice D, Barone S. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environmental Health Perspectives. 2000; 108(Suppl 3): 511-33.
5. Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. Lancet. 2006; 368(9553): 2167-78.
6. Neggers YH. Increasing Prevalence, Changes in Diagnostic Criteria, and Nutritional Risk Factors for Autism Spectrum Disorders. ISRN Nutrition. doi:10.1155/2014/514026.
7. Villagomez A, Ramtekkar U. Iron, Magnesium, Vitamin D, and Zinc Deficiencies in Children Presenting with Symptoms of Attention-Deficit/Hyperactivity Disorder. Children (Basel, Switzerland). 2014; 1(3): 261-79.
8. Arnold LE, Disilvestro RA, Bozzolo D, et al. Zinc for attention-deficit/hyperactivity disorder: placebo-controlled double-blind pilot trial alone and combined with amphetamine. Journal of child and adolescent psychopharmacology. 2011; 21(1): 1-19.
9. Wolowiec P, Michalak I, Chojnacka K, et al. Hair analysis in health assessment. Clin Chim Acta. 2013; 419: 139-71.
10. Franco-Pons N, Casanovas-Aguilar C, Arroyo S, et al. Zinc rich synaptic boutons in human temporal cortex biopsies. Neuroscience. 2000; 98(3): 429-35.
11. Gower-Winter SD, Levenson CW. Zinc in the central nervous system: From molecules to behavior. BioFactors (Oxford, England). 2012; 38(3): 186-93.
12. Wang Z, Li JY, Dahlstrom A, Danscher G. Zinc-enriched GABAergic terminals in mouse spinal cord. Brain research. 2001; 921(1-2): 165-72.
13. Brayer KJ, Segal DJ. Keep your fingers off my DNA: protein-protein interactions mediated by C2H2 zinc finger domains. Cell biochemistry and biophysics. 2008; 50(3): 111-31.
14. Fidalgo M, Shekar PC, Ang YS, et al. Zfp281 functions as a transcriptional repressor for pluripotency of mouse embryonic stem cells. Stem cells. 2011; 29(11): 1705-16.
15. Levenson CW, Morris D. Zinc and Neurogenesis: Making New Neurons from Development to Adulthood. Advances in Nutrition: An International Review Journal. 2011; 2(2): 96-100.
16. Sindreu C, Storm DR. Modulation of neuronal signal transduction and memory formation by synaptic zinc. Front Behav Neurosci. 2011;5:68.
17. Prado EL, Dewey KG. Nutrition and brain development in early life. Nutrition Reviews. 2014; 72(4): 267-84.
18. Pfaender S, Föhr K, Lutz AK, et al. Cellular Zinc Homeostasis Contributes to Neuronal Differentiation in Human Induced Pluripotent Stem Cells. Neural plasticity. 2016; 2016: 3760702.
19. Pang W, Leng X, Lu H, et al. Depletion of intracellular zinc induces apoptosis of cultured hippocampal neurons through suppression of ERK signaling pathway and activation of caspase-3. Neuroscience letters. 2013; 552: 140-5.
20. Adamo AM, Oteiza PI. Zinc deficiency and neurodevelopment: The case of neurons. BioFactors (Oxford, England). 2010; 36(2): 117-24.
21. Suh SW, Won SJ, Hamby AM, et al. Decreased Brain Zinc Availability Reduces Hippocampal Neurogenesis in Mice and Rats. Journal of Cerebral Blood Flow & Metabolism. 2009; 29(9): 1579-88.
22. Sun Y, Hu D, Liang J, et al. Association between variants of zinc finger genes and psychiatric disorders: Systematic review and meta-analysis. Schizophrenia Research. 2015; 162(1–3): 124-37.
23. Ohkubo N, Matsubara E, Yamanouchi J, et al. Abnormal Behaviors and Developmental Disorder of Hippocampus in *Zinc Finger Protein 521 (ZFP521) Mutant Mice*. PloS one. 2014; 9(3): e92848.
24. Golub MS, Keen CL, Gershwin ME. Moderate zinc-iron deprivation influences behavior but not growth in adolescent rhesus monkeys. The Journal of nutrition. 2000; 130(2S Suppl): 354s-7s.
25. Aggett PJ, Harries JT. Current status of zinc in health and disease states. Arch Dis Child. 1979; 54(12): 909-17.
26. Black MM. Zinc deficiency and child development. The American journal of clinical nutrition. 1998; 68(2 Suppl): 464s-9s.
27. Pfaender S, Sauer AK, Hagmeyer S, et al. Zinc deficiency and low enterocyte zinc transporter expression in human patients with autism related mutations in SHANK3. Scientific reports. 2017; 7: 45190.
28. Depciuch J, Sowa-Kucma M, Nowak G, et al. The role of zinc deficiency-induced changes in the phospholipid-protein balance of blood serum in animal depression model by Raman, FTIR and UV-vis spectroscopy. Biomedicine & pharmacotherapy 2017;89: 549-58.
29. Doboszewska U, Szewczyk B, Sowa-Kucma M, et al. Alterations of Bio-elements, Oxidative, and Inflammatory Status in the Zinc Deficiency Model in Rats. Neurotoxicity research. 2016; 29(1): 143-54.
30. Doboszewska U, Sowa-Kućma M, Młyniec K, et al. Zinc deficiency in rats is associated with up-regulation of hippocampal NMDA receptor. Progress in neuro-psychopharmacology & biological psychiatry. 2015; 56: 254-63.
31. Elbaz F, Zahra S, Hanafy H. Magnesium, zinc and copper estimation in children with attention deficit hyperactivity disorder (ADHD). Egyptian Journal of Medical Human Genetics. 2017; 18(2): 153-63.
32. Li SO, Wang JL, Bjorklund G, et al. Serum copper and zinc levels in individuals with autism spectrum disorders. Neuroreport. 2014; 25(15): 1216-20.
33. Eugene Arnold, Disilvestro R. Zinc in Attention-Deficit/Hyperactivity Disorder. Journal of child and adolescent psychopharmacology. 2005; 15(4): 619–27.
34. Tabatadze T, Zhorzholiani L, Kherkheulidze M, et al. Hair heavy metal and essential trace element concentration in children with autism spectrum disorder. Georgian medical news. 2015; (248): 77-82.
35. Lakshmi Priya MD, Geetha A. Level of trace elements (copper, zinc, magnesium and selenium) and toxic elements (lead and mercury) in the hair and nail of children with autism. Biological trace element research. 2011; 142(2): 148-58.
36. Blaurock Busch E, Amin OR, Rabah T. Heavy Metals and Trace Elements in Hair and Urine of a Sample of Arab Children with Autistic Spectrum Disorder. Mædica. 2011; 6(4): 247-57.
37. Skalny AV, Simashkova NV, Klyushnik TP, et al. Hair toxic and essential trace elements in children with autism spectrum disorder. Metabolic brain disease. 2017; 32(1): 195-202.
38. Al-Ayadhi LY. Heavy metals and trace elements in hair samples of autistic children in central Saudi Arabia. Neurosciences (Riyadh, Saudi Arabia). 2005; 10(3): 213-8.
39. Babaknejad N, Sayehmiri F, Sayehmiri K, et al. The Relationship between Zinc Levels and Autism: A Systematic Review and Meta-analysis. Iranian Journal of Child Neurology. 2016; 10(4): 1-9.

40. Starobrat-Hermelin B. [The effect of deficiency of selected bioelements on hyperactivity in children with certain specified mental disorders]. Ann Acad Med Stetin. 1998; 44: 297-314.

41. Tippairote T, Temviriyanukul P, Benjapong W, et al. Hair Zinc and Severity of Symptoms Are Increased in Children with Attention Deficit and Hyperactivity Disorder: a Hair Multi-Element Profile Study. Biological trace element research. 2017;179(2):185-194.

42. Bass DA, Hickok D, Quig D, et al. Trace Element Analysis in Hair: Factors Determining Accuracy, Precision, and Reliability. Alternative Medicine Review. 2001; 6(5): 472-81.

43. Buffoli B, Rinaldi F, Labanca M, et al. The human hair: from anatomy to physiology. International journal of dermatology. 2014; 53(3): 331-41.

44. Wolowiec P, Michalak I, Chojnacka K, et al. Hair analysis in health assessment. Clin Chim Acta. 2013; 419: 139-71.

45. Namkoong S, Hong SP, Kim MH, et al. Reliability on intra-laboratory and inter-laboratory data of hair mineral analysis comparing with blood analysis. Annals of dermatology. 2013; 25(1): 67-72.

46. RazaguiIbrahim IBA, Ghribi I. Maternal and neonatal scalp hair concentrations of zinc, copper, cadmium, and lead. Biological Trace Element Research. 2005; 106 (1): 1–27.

47. Yasuda H, Yoshida K, Yasuda Y, et al. Infantile zinc deficiency: Association with autism spectrum disorders. Scientific Reports. 2011; 1: 129.

48. Hyman SL, Stewart PA, Schmidt B, et al. Nutrient Intake From Food in Children With Autism. Pediatrics. 2012; 130(Suppl 2): S145-S153. doi:10.1542/peds.2012-0900L.

49. Marcinek K, Wójciak RW, Krejpcio Z, et al. An Assessment of the Consumption of Energy and Selected Minerals and Their Content in the Hair of Children Aged 1–4 Years. Biological Trace Element Research. 2016; 170: 255-263. doi:10.1007/s12011-015-0469-2.

50. Kang YJ. Metallothionein redox cycle and function. Experimental biology and medicine (Maywood, NJ). 2006; 231(9): 1459-67.

51. Richter P, Faroon O, Pappas RS. Cadmium and cadmium/zinc ratios and tobacco-related morbidities. Int J Environ Res Public Health. 2017; 14: 1154; doi:10.3390/ijerph14101154

52. Siwek M, Dudek D, Paul IA, et al. Zinc supplementation augments efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. J Affect Disord. 2009; 118(1-3): 187-95.

53. Ehninger D, Li W, Fox K, et al. Reversing Neurodevelopmental Disorders in Adults. Neuron. 2008; 60(6): 950-60.

54. Gibson RS, Hess SY, Hotz C, et al. Indicators of zinc status at the population level: a review of the evidence. Br J Nutr. 2008; 99 Suppl 3: S14-23.

55. de Benoist B, Darnton-Hill I, Davidsson L, et al. Conclusions of the Joint WHO/UNICEF/IAEA/IZiNCG Interagency Meeting on Zinc Status Indicators. Food and nutrition bulletin. 2007; 28(3 Suppl): S480-4.