Effects of chronic Zinc Fume exposure on memory and cognition

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ABSTRACT

Background: Purpose of present study was to investigate whether chronic exposure to zinc fume would affect serum zinc levels, memory, and cognition in zinc fume-exposed workers.

Methods: In a cross-sectional study, all zinc fume-exposed workers (exposed, n=20) were compared with unexposed workers (reference, n=20) matched for sex and education level in a zinc galvanization factory. The workers were undergone Wechsler Memory Scale (WMS) and Mini Mental State Examination (MMSE). Mean WMS score in exposed group (75.80 ± 14.40) was significantly lower than reference group (91.65 ± 15.79); however there was no significant difference in MMSE scores between two groups. There was a negative linear relationship between memory, MMSE scores, and serum zinc level. Exposure to zinc fume may lead to memory problems.

Conclusion: Regular measurement of serum zinc level is recommended for exposed individuals.

Key Words: Zinc, Memory, Cognition

INTRODUCTION

Zinc (Zn) is fourth most abundant intercellular metal and a biologically essential trace metal that is found in over 200 enzymes and proteins(1). Within central nervous system zinc is present in many areas of brain particularly in hippocampus and amygdale(2) manipulate brain structure and function(3). Hippocampus participates in spatial learning and memory and contains a higher concentration of Zn than any other regions of brain. Moreover zinc is an essential element for synapse formation, and structural plasticity (4).

Zn supplementation studies in infants and pregnant women have demonstrated benefits in terms of cognitive development of infants and babies born from mothers taking supplements (5-7).

Effects of Zn on cognitive function in older adults were evaluated in some studies as well. Ortega et al. examined 260 Spaniards aged 65–90 years and found that better cognitive scores were associated with greater dietary intake of a number of nutrients including Zn; suggesting that zinc may influence cognitive functions. However, authors have accredited that their design was unable to establish cause and effect relationship or to exclude possible confounding factors (8). Yaffe et al. run cognitive tests on 2166 adults aged 61–87 years, half of whom had been receiving Zn supplements (80 mg/d) for several years. There were no significant differences between groups but authors noted several limitations to their study, including lack of cognitive measures before supplementation, and loss of 40% of participants (9).

There have been fewer studies on Zn supplementation in children and adults and although improvements in cognitive function have been reported, methodological issues suggest that further data are required (10).

Attention has been also focused on possible adverse effects of elevated concentrations of zinc, which is known to play a major role in cell damage following stroke and may be a risk factor in Alzheimer's disease (AD), a pathological state which causes neuro-degeneration in some brain areas with great impairment of cognition(11, 12). Rats given short-term, high doses of zinc chloride (50 or

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100 mg/kg by gavages at 10% of body weight) had deficits in spatial learning(13). Cognitive deficits have also been reported in infants given zinc supplements 30 mg daily(14). This is potentially a concern because zinc is the most abundant and the most soluble transition metals in natural systems, and levels of zinc in natural waters, especially in reservoir sediments, are continuing to rise(15).

Workers involved in galvanizing, smelting, welding, or brass foundry operations are exposed to metallic zinc and zinc compounds. To protect workers, OSHA has set an average legal limit of 1 mg/ m^3 for zinc chloride fumes and 5 mg/m^3 for zinc oxide (dusts and fumes) in workplace air during an 8-hour workday, 40-hour work weekly. National Institute for Occupational Safety and Health (NIOSH) similarly recommends that level of zinc oxide in workplace air should not exceed an average of 1 mg/m^3 over a 10-hour period of a 40-hour work weekly (Agency for Toxic Substances and Disease Registry, Toxicological profile for Zinc, U.S. Department of Health and Human Services Public Health Service, August 2005).

To evaluate possible adverse effects associated with chronic zinc fume exposure in workplace, we decided to examine whether zinc fume exposure would affect memory, cognition and serum levels of zinc in current study.

MATERIALS AND METHODS

Population of present study consisted of all zinc galvanizing line workers in a zinc galvanization factory (exposed group), and workers involving in cutting and grinding metal part of the factory before galvanization section (reference group). Since all zinc fume-exposed workers (n=20) were evaluated, reference group (n=20) were matched for gender, education level, smoking status and alcohol consumption (Table 2). Workers of both groups were male. Shift work hour for workers was 12 hours daily.

Memory Assessment

Memory was assessed using Wechsler Memory Scale, 3rd ed. (WMS-III) [16]. Subtests of WMS-III were grouped into immediate memory, general memory, and working memory; all both auditory and visual. Many subtests are separated into two conditions: immediate condition and delayed condition which is run approximately 35 to 45 minutes after immediate condition. Following subsets, sums of scaled scores and index scores were derived and achieved: Auditory Immediate Memory, Visual Immediate Memory; Auditory Delayed Memory, Visual Delayed Memory, Auditory Recognition Delayed Memory; and Working Memory.

Cognitive Assessment

Global cognitive function was evaluated based on workers' score on Folstein Mini-Mental State Exam (MMSE) (17). Maximum score of MMSE is 30, and scores below 24 are suggestive of cognitive deficits (18).

Laboratory Measure

Blood samples from workers were sent to a reference laboratory for serum zinc level determination which was measured by flame atomic absorption spectrophotometry using a modification of method described by Kirgbright (19). Samples were kept on ice and transported to laboratory immediately where they were separated and aliquoted.

Procedures

Present work is supported by Department of Occupational Medicine; additionally was reviewed and approved by Institutional Ethics Committee of in Isfahan University of Medical Sciences. It was a cross-sectional study conducted in a zinc galvanization factory. An informed consent was obtained following a full explanation of procedures. All workers underwent a neuropsychological assessment included measurement of memory and cognition functions. Workers were interviewed and tested by a general physician, formally trained in procedures by department of psychiatry. General physician was unaware of participants' blood Zn concentrations (which were analyzed separately) and workers' groups (exposed or reference). Testing was scheduled to begin in same time of day (late morning to early afternoon) in both groups. All

participants were matched based on educational level, smoking habits, and alcohol consumption. Furthermore subjects were asked about their present and past medical history of acute or chronic diseases, and present and past history of medication intake. No workers suffered from neurodegenerative disease, or physical problem as a part of their clinical assessment each year.

Statistical analysis

Data are presented as mean ± SD or n (%) where appropriate. Independent sample t-test was performed to compare means of different variables (age, length of working in factory, serum zinc concentration; memory and MMSE scores) in two groups. Proportion of WMS-III and MMSE scores in different group of workers was compared using chi square test. For evaluation of relationships between serum zinc levels; memory or MMSE scores, Spearman correlation test was used. Statistical tests were two tailed and P values less than 0.05 were considered significant. All analyses were performed using SPSS software version 13.0.

RESULTS

Results showed that age of exposed and reference groups were not statistically different. However, there was a statistically significant difference between mean lengths of working in factory between two groups. Most workers in exposed group had employed less than five years, whereas in reference group most workers had employed 5-10 years. Data on age, working lengths in factory, smoking and educational status of the workers are presented in Table 1. Participants in both groups reported no history of alcohol drinking.

There was statistically significant difference between WMS-III scores in two groups (Table 2). Mean MMSE score in exposed group was less than reference group; however it was not statistically significant. Significantly higher serum zinc concentration was also found in exposed group compared to reference group (Table 2).

There was a negative linear relationship between serum Zn levels and WMS-III score (R, -0.49; P value = 0.004) or MMSE score (R, -0.38; P value = 0.024).

Results of WMS-III scores were organized into summary index scores, reflecting Verbal, Visual, Immediate and Working memory and interpreted as following: 130 and above as very superior abilities; 120-129 superior; 110-119 high average abilities; 90-109 average abilities; 80-89 low average; 70-79 borderline abilities; and 69 and below considered as impairment. Differences in proportions of WMS-III scores in different groups of workers were statistically significant (Table 3).

Following categories for MMSE scores were also established: severely impaired 11; moderately to severely impaired 19; mildly to moderately impaired 20-24; possibly mild to moderately impaired 25-27; and possibly normal 28-30. Results regarding proportions of MMSE scores among workers shown in Table 4. Differences in proportions of MMSE scores in two groups of workers were not statistically significant.

Table 1: Comparison of different variables including age and working lengths in the factory in exposed and reference groups.

Variables	Reference	Exposed	P-Value
Age (year) (Mean ± SE)	32.65 ± 1.33	35.20 ± 1.51	0.214
Working lengths in the factory (Mean ± SE)	7.11 ± 0.92	4.74 ± 0.66	0.045

SE, Standard error of mean;

Table 2: Comparison of Serum Zn concentration, WMS-III score, MMSE score in exposed and reference groups.

Variables	Mean ± SD	P-Value
Serum Zn concentration (µg/ml)		
Reference	74.10 ± 8.21	<0.001
Exposed	112.50 ± 7.59	
WMS-III score		
Reference	91.65 ± 15.79	0.002
Exposed	75.80 ± 14.40	
MMSE score		
Reference	24.50 ± 1.00	0.058
Exposed	23.70 ± 1.52	

SD, Standard deviation; WMS-III, Wechsler Memory Scale, 3rd version; MMSE, Mini-Mental State Exam, Zn, Zinc

Table 3: Proportion of WMS-III score among worker

		Reference	Exposed	P Value
WMS-III Score	< 69	2 (10)	8 (40)	0.04
	70-79	1 (5)	4 (20)	
	80-89	5 (25)	4 (20)	
	90-109	11 (55)	4 (20)	
	110-119	1 (5)	0	
Total		20 (100)	20 (100)	

Data are presented as n (%).
WMS-III, Wechsler Memory Scale, 3rd version

Table 4: Proportion of MMSE score among workers

		Reference	Exposed	P value
MMSE Score	20-24	6 (30)	12 (60)	0.057
	25-27	14 (70)	8 (40)	
Total		20 (100)	20 (100)	

Data are presented as n (%).
MMSE, Mini-Mental State Exam,

DISCUSSIONS

Current study suggests that chronic Zn fume exposure may be associated with memory impairments. Results show that Zn fume exposure in zinc galvanization factory led to increased levels of serum zinc concentration and impairment in memory of exposed workers. To the best knowledge of authors, there has not been any previous study on

memory problems and Zn exposure; however study by Flinn et al., showed enhanced zinc consumption cause memory deficits and increased brain levels of zinc in rat(20). Zinc is involved in developmental regulation of neurotrophins and N-methyl-D-aspartate (NMDA) receptors, controlling use of glutamate as a neurotransmitter in central nervous system (CNS)(21). This is particularly important in hippocampus; a region of brain involved in learning and memory. It is an intriguing link to role of zinc in neuropsychological development(21). Other contaminants in galvanizing factory may be also involved in reducing memory which was not evaluated in our study (22); for example developing motor and intellectual skills require zinc and iron (23).

Although relationship between serum Zn level and memory score was not strong, it

might support the idea that Zn fume exposure is an effective factor on memory impairment.

Statistical data analysis shows that MMSE scores were not statistically different between the groups with p value of 0.058; however this could be due to small sample size.

During past decade, many trials were performed to evaluate effects of postnatal zinc supplementation on mental and psychomotor development during infancy and childhood; however these investigations have provided conflicting results. Kirksey et al.(24) reported positive relation between intake of estimated available dietary zinc during pregnancy with neonatal behavior and motor development. Merialdi et al. (25) evaluated effect of zinc supplementation during pregnancy on neurobehavioral development of fetuses in Peruvian women. They found that zinc supplementation led to fewer episodes of minimal fetal heart rate variability and increases in fetal movement.(25) In contrast to these, results of a study in Bangladesh showed that zinc enrichment led to reductions in cognitive performance in infants given zinc supplements(14). Findings by Hamadani et al. consistent with Black et al. (26) showed no direct effects of zinc supplementation on infant development or behavior at either 6 or 10 months; our results also showed that exposure to zinc fume may have negative effects on memory and cognition(14,26).

In an effort to assess effects of zinc supplementation on cognitive function of an adult population, Simpson and co workers reported an age- and gender-related effect on cognitive functioning(22). In our study, all workers in both groups were male and young.

It has been demonstrated that interpretation of MMSE scores depends on person's age and education level (27). However in our study exposed and reference groups had been matched for sex and education level and there was not a significant difference between mean ages of groups. Mental disorders can lead to abnormal findings on MMSE testing; as well as presence of purely physical problems. In our study no workers suffered from physical or mental problems, as revealed by their clinical assessment.

We found a significant but relatively weak correlation between serum Zn level and WMS and MMSE scores which may be indeed due to one of many possible confounding factors.

The above findings direct authors to suggest a possible role of chronic zinc fume exposure in pre-clinical memory impairment. Authors raise question whether pre-clinical detection of zinc neurotoxicity and consequent early treatment might help to prevent or retard onset of different central nervous system pathologies.

present study has some limitations:

1- As a major limitation, we did not measure other neurotoxic metals in working environment and biological fluids. It is reported that technical grade zinc used in galvanization process has about 1.0 to 20.0 ppm lead as impurity.

2- We did a biologic monitoring; however failure to characterize zinc fume exposure (particle/fume size, composition, and aerosol concentrations) is a shortage in our study.

3- Although all zinc fume exposed workers were evaluated (n=20), sample size in this study is too small to be able to confirm definitely effect of zinc fume inhalation on memory. Studies with larger sample sizes are necessary to corroborate results of current study.

4- Certain zinc galvanization processes may also result in co-exposure to chromium, iron (steel), and other metals which were not evaluated in our study. However, relationship between serum Zn level and memory score might support that part of memory impairment may be due to Zn fume exposure.

5- The subjects were not randomly assigned in each group. Assignment in two studied groups was based on their ability and special skills, which may be related to mental capacity. It may be possible that less skilled workers had been hired in areas of higher exposure.

Therefore, although we measure WMS and MMSE scores on workers to find relationship between serum Zn levels and memory or cognition, the above limitations could affect the scores of the tests. A dose response study with larger sample size is recommended to confirm these findings.

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REFERENCES

1. Ebadi M, Pfeiffer R. Zinc in neurological disorders and in experimentally induced epileptiform seizures. In: Frederickson CJ, Howell G, Kasarkis E, (eds). The Neurobiology of Zinc, Part B: Deficiency, Toxicity and Pathology. New York, Alan R, Liss, 1984: 307–324.
2. Takeda A. Movement of zinc and its functional significance in the brain. Brain Res Rev 2000 34: 137–148.
3. Sandstead HH. Zinc is essential for brain development and function. J Trace Elem Exp Med 2003;16: 165–173.
4. Grabrucker AM, Knight MJ, Proepper C, Bockmann J, Joubert M, Rowan M, Nienhaus GU, Garner CC, Bowie JU, Kreutz MR, Gundelfinger ED, Boeckers TM. Concerted action of zinc and ProSAP/Shank in synaptogenesis and synapse maturation. EMBO J. 2011 Jan 7.
5. Black MM. Zinc deficiency and child development. Am J Clin Nutr 1998;68: 464S–469S.
6. Bhatnagar S, Taneja S. Zinc and cognitive development. Br J Nutr 2001;85:S139–S145.
7. Salgueiro MJ, Zubillaga MB, Lysionek AE, Caro RA, Weill R, Boccio JR. The role of zinc in the growth and development of children. Nutrition 2002;18: 510–519.

8. Ortega RM, Requejo AM, Andre´s P, Lo´pez-Sobaler AM, Quintas ME, Redondo MR, Navia B & Rivas T. Dietary intake and cognitive function in a group of elderly people. Am J Clin Nutr 1997; 66: 803–809.
9. Yaffe K, Clemons TE, McBee WL, Lindblad AS. Impact of antioxidants, zinc, and copper on cognition in the elderly: a randomized, referenceled trial. Neurology 2004;63: 1705–1707.
10. Penland JG. Behavioral data and methodology issues in studies of zinc nutrition in humans. J Nutr 2000;130: 361S–364S.
11. Koh JY, Suh SW, Gwag BJ, He YY, Hsu CY, Choi DW. The role of zinc in selective neuronal death after transient global ischemia. Science 1996; 272:1013–1016.
12. Danscher G, Jensen KB, Frederickson CJ, et al. Increased amounts of zinc in the hippocampus of Alzheimer's diseased brains: a proton-induced X-ray emission spectroscopic analysis of cryostat sections from autopsy material. J Neurosci Methods 1997; 76:53–59.
13. Turner TY, Soliman MR. Effects of zinc on spatial reference memory and brain dopamine (D1) receptor binding kinetics. Prog Neuropsychopharmacol Biol Psychiatry 2000; 1203:17–24.
14. Hamadani JD, Fuchs GJ, Osendarp SJ, Huda SN, Grantham-McGregor SM. Zinc supplementation during pregnancy and effects on mental development and behavior of infants: a follow-up study. Lancet 2002; 360: 290–294.
15. Bricker OP, Jones BF. Main factors affecting the composition of natural waters. In: Salbu B, Steinnes E, (eds). Trace Elements in Natural Waters. Boca Raton, FL, CRC Press, 1995: 1–20.
16. Wechsler D. Manual for wechsler memory scale, revised. San Antonio, TX, Psychological Corporation, 1987.
17. Folstein M, Folstein S, McHuth P. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
18. Lesser IM, Banyas C. Depression. In: Osterweil D, Brummel-Smith K, Beck JC, (eds). Comprehensive Geriatric Assessment. New York, McGraw-Hill, 2000:474–475.
19. Kirgbright GF. Atomic absorption spectroscopy. Elemental analysis of biological materials. Vienna Technical Report Series. Int Atomic Agency 1980; 197:141–165.
20. Flinn JM, Hunter D, Linkous DH, Lanzirotti A, Smith LN, Brightwell J, Jones BF. Enhanced zinc consumption causes memory deficits and increased brain levels of zinc. Physiol Behav 2005;83(5):793-803.
21. Levenson CW. Regulation of the NMDA receptor: implications for neuropsychological development. Nutr Rev 2006; 64(9):428-32.
22. Railey AM, Groeber CM, Flinn JM.The Effect of Metals on Spatial Memory in a Transgenic Mouse Model of Alzheimer's Disease. J Alzheimers Dis. 2011 Jan 14.
23. Christian P, Murray-Kolb LE, Khatry SK, Katz J, Schaefer BA, Cole PM, Leclerq SC, Tielsch JM. Prenatal micronutrient supplementation and intellectual and motor function in early school-aged children in Nepal. JAMA. 2010 Dec 22; 304(24):2716-23.
24. Kirksey A, Wachs TD, Yunis F, et al. Relation of maternal zinc nutriture to pregnancy outcome and infant development in an Egyptian village. Am J Clin Nutr 1994; 60:782–92.
25. Merialdi M, Caulfield LE, Zavaleta N, Figueroa A, DiPietro JA. Adding zinc to prenatal iron and folate tablets improves fetal neurobehavioral development. Am J Obstet Gynecol 1998; 180:483–490.
26. Black MM, Sazawal S, Black RE, Khosla S, Kumar J, Menon V. Cognitive and Motor Development Among Small-for-Gestational-Age Infants: Impact of Zinc Supplementation, Birth Weight, and Caregiving Practices. Pediatrics 2004; 113(5):1297-1305.
27. Simpson EE, Maylor EA, Rae G, et al. Cognitive function in healthy older European adults: the ZENITH study. Eur J Clin Nutr 2005; 59(Suppl 2):S26-30.