Curr Pediatr Res 2013; 17 (2): 79-83 ISSN 0971-9032
http://www.pediatricresearch.info

Levels of heavy metal and trace element among children with Autism spectrum disorders.

Adel Almogren[1], Zahid Shakoor[2], Abdulkareem Almomen[3], Rana M.W. Hasanato[4]

[1]Department of Pathology, College of Medicine and University Hospitals, King Saud University, PO Box: 2925 Riyadh 11461, Kingdom of Saudi Arabia
[2]Department of Pathology, College of Medicine and University Hospitals, King Saud University, Riyadh, Kingdom of Saudi Arabia
[3]Department of Medicine, Division of Hematology / Oncology, College of Medicine and University Hospitals, King Saud University, Riyadh, Kingdom of Saudi Arabia
[4]Department of Biochemistry, College of Medicine and University Hospitals, King Saud University, Riyadh, Kingdom of Saudi Arabia

Abstract

Persistent exposure to high levels of heavy metals and trace elements has been implicated in autism spectrum disorders (ASDs). This study was performed to investigate the levels of heavy metals and trace elements in hair samples of patients with ASDs. Retrospective analysis of data from 58 children with ASDs with the mean age of 6.31±4.12 years between Jan. 2004 and Oct. 2008 was performed at King Khalid University Hospital, Riyadh. Hair samples were sent to Micro Trace Mineral Gmbh, Laboratory for Clinical and Environmental Analysis, Hersbruck, Germany for heavy metals and trace elements analysis. Acceptable laboratory reference ranges were used for interpretation of results. Majority of the children (93.1%) were males. Among the 13 heavy metals and trace elements detected in higher concentrations uranium was present in 23 (39.6%), tellurium in 21 (36.2%), mercury in 15 (25.8%), strontium in 15 (25.8%), aluminum in 14 (24.1%) and nickel in 12 (20.6%) patients. High levels of heavy metals and trace elements detected in Saudi children with ASDs indicate environmental exposure. Further investigations are recommended for assessment of the environmental hazard in the region.

Keywords: Autism, Heavy metals, Mercury, Trace elements, Uranium.

Accepted March 06 2013

Introduction

Autism spectrum disorders (ASDs) are neurodevelopmental childhood disorders of unknown etiology characterized by impaired verbal and nonverbal communication and social interactions associated with stereotyped patterns of behavior and interests [1]. Genetic and environmental factors have been implicated in the disorder [2]. Exposure to heavy metals because of their potential to cause developmental neurotoxicity is believed to be among the major risk factors [3,4]. Differential expression of a large number of genes has be shown to correlate with blood levels of lead and mercury in children with ASD [5,6]. High blood levels of mercury during various developmental stages consequent to genetically reduced ability to excrete mercury has been shown to cause immunological, neurological and behavioral abnormalities very similar to those seen in ASDs [7-9]. The likelihood of a combination of genetic and environmental factors especially exposure to metals in the etiology of ASDs therefore appears to be strong and cannot be ignored.

Because of the widespread environmental contamination of heavy metals it is rather difficult to avoid persistent exposure to metals. Although lead, cadmium, arsenic and aluminum have been implicated in ASDs but the evidence supporting mercury as an etiological agent is more convincing [10,11]. A study investigating relationship between autism symptoms and body burden of toxic metals has revealed a significant positive association between the severity of autism and the relative body burden of toxic metals [12]. These observations gain further support from the fact that following chelation therapy for removal of heavy metals from the body almost all the patients with autism have been shown to exhibit clinical improvement [13]. It is therefore quite conceivable that apart from their

role as etiological agents persistent exposure to metals may also contribute to the clinical manifestations of ASDs. This study retrospectively examines the results of heavy metal and trace element screening of children with ASDs at King Khalid University Hospital in Riyadh.

Methods

After obtaining the departmental approval data were collected from the records of 58 Saudi patients with ASDs at King Khalid University Hospital. The patients were screened for the presence of heavy metals and trace elements during the period between 2004 and 2008. This group of patients included 54 male and 4 female patients with the mean age of 6.31±4.12 years (range 2-18 years). The diagnosis of ASD was made in accordance with the standardized criteria provided in the American Psychiatric Association's Diagnostic and Statistical Manual-IV.

Hair samples from the patients were obtained close to scalp from the occipital area in a biohazard bag. The samples were sent to Micro Trace Mineral Ghmb, Laboratory for Clinical and Environmental Analysis, Hersbruck, Germany for the estimation of heavy metals and trace elements. Briefly, the analytical procedure involved repeated washing of hair samples with de-ionized detergent followed by rinsing of the samples with de-ionized water and drying in a specially-designated oven before weighing. The samples were then digested with certified metal-free acids in a closed-vessel microwave digestion system. Ultrapure water was used for final sample dilution and the analysis was performed by inductively coupled plasma with mass spectrometry (ICP-MS) utilizing collision/reaction cell methods coupled with ion-molecule chemistry. Certified hair standards and in-house standards were used as part of the laboratory validation of results. This being a retrospective study lacking normal controls the results were interpreted by comparing patient data with the normal laboratory reference ranges.

Results

The majority of the children with ASDs (81%) were either equal to or less than seven years of age. Male preponderance was evident as 93.1% of the total children investigated were male. Fig 1 describes the pattern of various heavy metals and trace elements detected above the acceptable laboratory limits in hair samples from patients with ASDs. Out of the 58 patients investigated the highest number of patients 23 (39.6%) were found to have increased levels of uranium. The other remarkable findings were 21 (36.2%) patients with high levels of tellurium followed by mercury in 15 (25.8%), strontium in 15 (25.8%), aluminum in 14 (24.1%) and nickel in 12 (20.6%) patients. Table 1 shows data for the detection range and the mean concentration of each heavy metal and trace element expressed as parts per million that were found to be higher than the acceptable laboratory limits in the patients.

This article may be cited as:
Almogren A, Shakoor Z, Almomen A, Hasanato RMW. Levels of heavy metal and trace element among children with Autism spectrum disorders. Curr Pediatr Res 2013; 17 (2): 79-83.

Table 1. *Analysis of heavy metals and trace elements in 58 patients with Autism Spectrum Disorders*

S. No.	Element	No. (%)	Minimum	Maximum	Mean ± sd	Acceptable Range
1.	Aluminum	14 (24.1)	8.250	16.940	11.5433 ± 2.5609	<8.00
2.	Antimony	6 (10.3)	0.650	0.850	0.6505 ± 0.12889	<0.60
3.	Bismuth	4 (6)	0.480	3.200	2.1838 ± 1.30223	<0.270
4.	Lead	3 (5)	3.910	5.400	4.9023 ± 0.86198	<3.00
5.	Mercury	15 (25.8)	0.700	17.620	2.0899 ± 4.31575	<0.60
6.	Nickel	12 (20.6)	0.520	3.920	1.5988 ± 0.90869	<0.50
7.	Silver	4 (6)	0.820	2.860	1.3582 ± 1.00066	<0.700
8.	Tantalum	7 (12)	0.012	0.300	0.0614 ± 0.10621	<0.011
9.	Tellurium	21 (36.2)	0.012	0.040	0.0283 ± 0.01374	<0.010
10.	Tin	3 (5)	0.880	1.210	1.0990 ± 0.19226	<0.700
11.	Uranium	23 (39.6)	0.090	0.910	0.3500 ± 0.24694	<0.080
12.	Iodine	2 (3.4)	9.510	9.510	9.5100 ± 0.00000	<4.650
13.	Strontium	15 (25.8)	4.930	36.760	14.900 ± 10.9839	<4.280

Levels of heavy metals and trace elements expressed as parts per million (ppm)

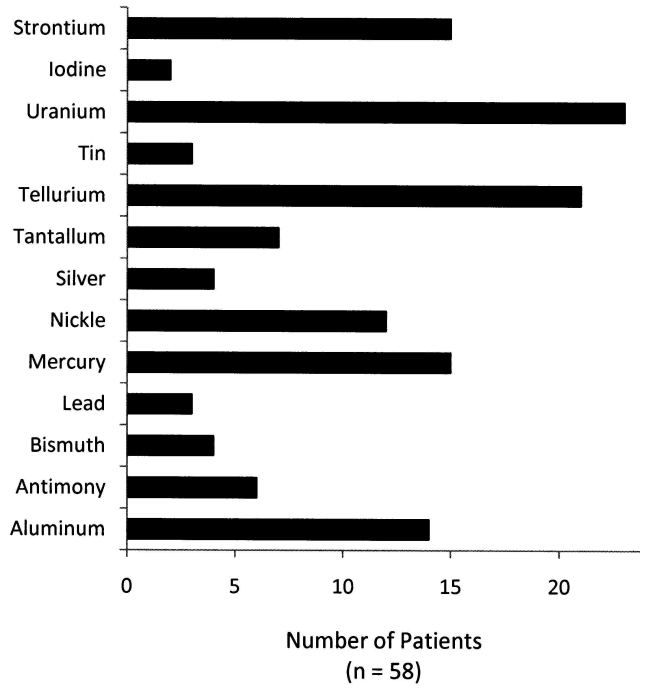

Figure 1. *Pattern of heavy metal and trace element distribution above the normal acceptable levels in parts per million (ppm) among children with Autism Spectrum Disorders.*

Discussion

The most remarkable observation in the present study was detection of high levels of uranium in the hair samples from almost 40% of children with ASDs. In addition varying proportions of the patients were also found to have increased levels of other metals. Data regarding detection of uranium in autistic children are scarce. A study from Kuwait comparing levels of toxic metals in hair samples from children suffering from autism with normal counterparts found significantly high levels of lead, mercury and uranium in autistic children [14]. Animal studies using embedded depleted uranium fragments have shown that uranium exhibits predilection for hippocampus as a site for its retention in the central nervous system and is a potent inducer of electro-physiological changes [15]. Similarly, experiments performed on neonatal rats using radioactive uranium (^{235}U) have clearly demonstrated uranium induced adverse effects on growth and behavior along with the induction of biochemical changes in the brain [16]. Exposure to uranium especially in the early child hood may therefore because of its chemical and radiational effects could contribute to neuro-developmental abnormalities associated with ASDs.

Depleted uranium a by-product of uranium enrichment is relatively less radioactive compared to natural uranium [17]. Apart from its wide range of military applications depleted uranium is commonly used in glassware, ceramics, containers and in radiation shields in medical equipment [18,19]. Evidence of exposure to depleted uranium during the Gulf War I through inhalation of depleted uranium aerosol detected in the war veterans until nine years after the war [20] indicates a significant environmental hazard. A recently published review addressing the use of depleted uranium in Gulf war has linked exposure to depleted uranium with emergence of a relatively more aggressive form of Kaposi sarcoma in Southern Iraq [21]. Although controversies still surround the impact of use of depleted uranium in the Gulf war the detection of higher concentration of uranium in the solid particulate matter in surface air in Kuwait [22] appears to important. This may not only be relevant to the observations made in the present study but could be very significant particularly in the backdrop of a study reporting high levels of uranium in children with autism in Kuwait [14].

A significant number of children in the present study had high levels of mercury in their hair samples. A number of studies point to a link between autism and mercury exposure especially in the early years of life [23-25]. Higher level of mercury has been found in baby teeth and blood of autistic children [26]. Similarly, strikingly high levels of hair mercury have been reported among four to seven years old boys from Kuwait [14]. In contrast to these findings significantly low levels of mercury in the first baby haircuts of children with autism have also been reported [27]. It is possible that impaired elimination of mercury in autistic children may result in accumulation of mercury to toxic levels over the years. In line with these observations repeated administration of vaccines with mercury containing preservative thiomersal to autistic children may pose a serious threat of neurtoxicity. This was evident in animal studies that following injection of thimersal containing vaccines compared to blood levels significantly higher concentration of mercury was found in the brain tissues and it was postulated the it may remain at markedly high levels for months and years because of repeated vaccinations [28]. Aluminum commonly used as an adjuvant in vaccines has also been implicated in neurtoxicity in a number of studies [29-31]. Detection of high levels of aluminum in children with ASDs (24.1%) in the present study could be relevant to the associated neurological deficit.

High levels of tellurium were also detected in the hair samples of over 36% of the children with ASDs in this study. Little is known about the role of tellurium in ASDs and the relevant data are lacking. It is a non-essential trace element and its biological role has not been clearly established to date. The inorganic and organic tellurium derivatives have been shown to be highly toxic for the central nervous system in rodents [32]. In addition these derivatives are also capable of causing a marked reduction in cholesterol biosynthesis resulting in degradation of myelin causing demyelination of peripheral nerves [33]. The neurotoxicity associated with tellurium and its derivatives may therefore contribute to neurological abnormalities in ASDs. Similarly there are no data available on

the role of strontium in ASDs a trace element that has also been considered to have a potential to cause neurological damage [34].

Increased levels of metals and trace elements in hair samples from Saudi children with ASDs have been reported in the past [35]. Compared to the findings of the present study the previous study did not measure uranium, lead levels were found to be high whereas only three children in the present study had high lead levels. Nickel was found to be high in 20.6% of the children in the present study which was reported to be lower than the controls in the previous study. Similarly cadmium and arsenic were significantly high in the previous study whereas none of the patients in the present study was found to have high levels of these two elements. The differences in these two studies form the Kingdom of Saudi Arabia could be due to regional variation as the previously reported study was from the central part of the Kingdom whereas this information in the present study could not be retrieved.

Conclusion

A number of important observations were made in the present study regarding the heavy metals and trace elements analysis in the hair samples of the children with ASDs that may reflect the environment exposure. Being a retrospective analysis the study was however limited by the lack of matching controls. Large scale prospective studies for assessment of heavy metals and trace elements are recommended for further evaluation of Saudi children with ASDs particularly in the back drop of high levels of uranium in a sizeable number of patients detected in the present study.

Acknowledgements

The authors would like to thank Dr. Eleonore Blaurock-Busch. PhD / Micro Trace Minerals GmbH, Hersbruck, Germany for her assistance in the analysis of hair samples.

References

1. American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC:American Psychiatric Association.
2. Hertz-Picciotto I, Croen LA, Hansen R, Jones CR, van de Water J, Pessah IN. The CHARGE study: an epidemiologic investigation of genetic and environmental factors contributing to autism. Environ Health Perspect 2006; 114: 1119-1125
3. Tchounwou PB, Ayensu WK, Ninashvili N, Sutton D. Environmental exposure to mercury and its toxicopathologic implications for public health. Environ Toxicol 2003; 18: 149-175.
4. Clarkson TW, Magos L. The toxicology of mercury and its chemical compounds. Crit Rev Toxicol 2006; 36: 609-662.
5. Tian Y, Green PG, Stamova B, Hertz-Picciotto I, Pessah IN, Hansen R, et al. Correlations of gene expression with blood lead levels in children with autism compared to typically developing controls. Neurotox Res 2011; 19: 1-13.
6. Stamova B, Green PG, Tian Y, Hertz-Picciotto I, Pessah IN, Hansen R, et al. Correlations between gene expression and mercury levels in blood of boys with and without autism. Neurotox Res 2011; 19: 31-48.
7. Austin D. An epidemiological analysis of the 'autism and mercury poisoning' hypothesis. Int J Risk Saf Med 2008; 20: 135-142.
8. Geier DA, King PG, Geier MR. Mitochondrial dysfunction, impaired oxidative-reduction activity, degeneration, and death in human neuronal and fetal cells induced by low-level exposure to Thimerosal and other metal compounds. Toxicol Environ Chem 2009; 91: 735-749.
9. Geier DA, King PG, Sykes LK, Geier MR. A comprehensive review of mercury provoked autism. Indian J Med Res 2008; 128: 383-411.
10. Kidd PM. Autism, an extreme challenge to integrative medicine. Part 1. The knowledge base. Altern Med Rev 2002; 7: 292-316.
11. Bernard S, Enayati A, Redwood L, et al. Autism: a novel form of mercury poisoning. Med Hypotheses 2001; 56: 462-471.
12. Adams JB, Baral M, Geis E, Mitchell J, Ingram J, Hensley A, et al. The severity of autism is associated with toxic metal body burden and red blood cell glutathione levels. J Toxicol 2009; 2009: 532640.doi:-10.1155/2009/532640
13. Kirkman Laboratories. Detoxification of heavy metals in the treatment of autism. In: A Guide to Scientific Nutrition for Autism and Related Conditions. Lake Oswego, OR: Kirkman Laboratories; 2002.
14. Fido A, Al-Saad S. Toxic trace elements in the hair of children with autism. Autism 2005; 9: 290-298.
15. Pellmar TC, Keyser DO, Emery C, Hogan JB. Electrophysiological changes in hippocampal slices isolated from rats embedded with depleted uranium fragments. Neurotoxicology 1999; 20: 785-792.
16. Gu G, Zhu S, Wang L, Yang S. Irradiation of 235 uranium on the growth, behavior and some biochemical changes of brain in neonatal rats [in Chinese]. Wei Sheng Yan Jiu 2001; 30: 257-259.
17. Craft E, Abu-Qare A, Flaherty M, Garofolo M, Rincavage H, Abou-Donia M. Depleted and natural uranium: chemistry and toxicological effects. J Toxicol Environ Health B Crit Rev 2004; 7: 297-317.
18. Giannardi, C. and Dominici, D. Military use of depleted uranium: assessment of prolonged population exposure. J. Environ Radioact 2003; 64: 227-236.
19. Betti, M. Civil use of depleted uranium. J. Environ Radioact. 2003; 64: 113-119.
20. Durakoviæ A, Horan P, Dietz LA, Zimmerman I. Estip

mate of the time zero lung burden of depleted uranium in Persian Gulf War veterans by the 24-hour urinary excretion and exponential decay analysis. Mil Med 2003; 168: 600-605.
21. Shelleh HH. Depleted uranium: Is it potentially involved in the recent upsurge of malignancies in populations exposed to war dust? Saudi Med J 2012; 33: 483-488.
22. Bem, H, Bou-Rabee F. Environmental and health consequences of depleted uranium use in the 1991 Gulf War. Environ Int 2004; 30: 123-134.
23. Mutter J, Naumann J, Schneider R, Walach H, Haley B. Mercury and autism: accelerating evidence? Neuro Endocrinol Lett. 2005; 26: 439-446.
24. Geier DA, Geier MR. A meta–analysis epidemiological assessment of neurodevelopmental disorders following vaccines administered from 1994 through 2000 in the United States. Neuro Endocrinol Lett 2006; 27: 401–413.
25. Palmer RF, Blanchard S, Wood R. Proximity to point sources of environmental mercury release as a predictor of autism prevalence. Health Place 2009; 15: 18-24.
26. Adams JB, Romdalvik J, Ramanujam VM, Legator MS. Mercury, lead, and zinc in baby teeth of children with autism versus controls. J Toxicol Environ Health A 2007; 70: 1046-1051.
27. Adams JB, Romdalvik J, Levine K E, Hu LW. Mercury in first -cut baby hair of children with autism versus typically-developing children. Toxicol Environ Chem 2008; 90: 739-753.
28. Burbacher TM, Shen DD, Liberato N, Grant KS, Cernichiari E, Clarkson T. Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing thimerosal. Environ Health Perspect 2005; 113: 1015-1021.
29. Crapper DR, Krishnan SS, Dalton AJ. Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. Science 1973; 180: 511-513.
30. Kawahara M, Kato M, Kuroda Y. Effects of aluminum on the neurotoxicity of primary cultured neurons and on the aggregation of beta-amyloid protein. Brain Res Bull 2001; 55: 211-217.
31. Shaw CA, Petrik MS. Aluminum hydroxide injections lead to motor deficits and motor neuron degeneration. J Inorg Biochem. 2009; 103: 1555-1562.
32. Maciel EN, Bolzan RC, Braga AL, Rocha JB. Diphenyl diselenide and diphenyl ditelluride differentially affect delta-aminolevulinate dehydratase from liver, kidney, and brain of mice. J Biochem Mol Toxicol. 2000; 6: 310-319.
33. Goodrum JF. Role of organotellurium compounds in neuropathy. Neurochem Res 1998; 23: 1313-1319.
34. Huang J, Wu J, Li T, Song X, Zhang B, Zhang P, et al. Effect of exposure to trace elements in the soil on the prevalence of neural tube defects in a high-risk area of China. Biomed Environ Sci 2011; 24: 94-101.
35. Al-Ayadhi LY. Heavy metals and trace elements in hair samples of autistic children in central Saudi Arabia. Neurosciences. 2005; 10: 213-218.

Correspondence to:

Adel Almogren
Department of Pathology
College of Medicine and University Hospitals
King Saud University
PO Box: 2925, Riyadh 11461
Kingdom of Saudi Arabia