TOXIC EFFECT OF SOME METALS ON LANGUAGE DEVELOPMENT IN A SAMPLE OF CHILDREN IN SOHAG GOVERNORATE

BY

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ABSTRACT

Chronic exposure to metals has subtle toxic effect on the nervous system in early childhood. It may cause impairment of language and learning development. The aim of the present study is to estimate the level of some metals (copper, lead, cadmium, manganese, and zinc) in blood samples of children having delayed language development without any obvious causes and to assess the relationship between those metals and their toxic effect on language development. The current work was conducted on 60 children having language disorder and 40 normal healthy cases taken as controls. All studied cases were subjected to full history, general examination, vocal tract examination and neurological examination. The children were assessed clinically by many tests such as; Stanford Binet test, Vineland Social Maturity Scale and Arabic language test. Evaluation of peripheral hearing was done by tympanometry and pure tone audiometry. The level of metals in the blood of the studied cases was estimated by Inductively Coupled Plasma Mass Spectrometry (ICP-MS).The diseased children showed significant retardation of language development associated with decreased IQ levels and delayed development of other body activities such as sitting, walking and talking. In addition, the level of the studied metals, especially lead was higher in the diseased children than in the normal group. The diseased cases showed a statistically significant higher lead level than the healthy cases (mean values were 22.33 ± 1.27μg/dl and 8.57 ± 1.39 μg/dl respectively). It can be concluded that elevated level of blood metals in children might affect language development as well as the development of other body activities. It is recommended to measure the blood level of metals in early childhood and try to manage cases with high levels and follow up them by clinical and laboratory examination to avoid delayed language development.

Keywords: *Metals, Lead, Language development, IQ.*

INTRODUCTlON

The effect of chemicals on the nervous system has been recognized since ancient times. It was recognized that even small doses of some chemicals result in subtle nervous system impairments that affect an individual's performance (Gilbert, 2008).

Heavy metal pollution can arise from many sources e.g., the smelting of copper and the preparation of nuclear fuels. Electroplating is the primary source of chromium and cadmium. Cadmium, lead and zinc are released in tiny particulates as dust from rubber tires on road surfaces. The small size allows these toxic metals to rise on the wind to be inhaled, or transported onto topsoil or edible plants (Park et al., 2011).

Exposure to metals causes impairment of language and learning. There are four heavy metals have the greatest affection on language: lead, mercury, arsenic and aluminum. Lead is so common in our industrialized environment. In fact, lead exposure is the third most common hazardous occupational exposure. Some occupations put employees and their families at particularly high risk including lead smeltering, stained glass making, paint manufacturing and radiator repair. Non-occupational sources of exposure include contamination from nearby industry or railways, lead-containing paint or plumbing in old buildings, and use of imported glazed ceramics (Weizsaecker, 2003).

Lead can affect language by impairment of cognition (Lindgren et al., 1996), auditory attention (Bruce et al., 2000), intellectual function (Ide and Parker, 2005), hearing (Chuang et al., 2007) and impairment of reading, behavior and memory attention (Nigg et al., 2008).

Other metals such as manganese (Mn) may be also incriminated in delayed language development. Wright et al. (2006) found that children's general intelligence scores, particularly verbal IQ scores, were significantly related, inversely, to hair Mn. Decrease in Copper (Cu) level incriminates in development of stuttering (Pesak and Opavsky, 2000 and Alm, 2005). Also decreased copper level was found in Gilles de la tourette syndrome (Robertson et al., 1987). Copper is significantly depleted in Alzheimer's disease neocortex (Schrag et al., 2011).

Moreover, deficiency of zinc can cause affection of language. Grant (2004) reported that dyslexic children showed severe zinc-deficiency in their sweat.

The aim of the present study is to estimate the level of some metals (copper, lead, cadmium, manganese, and zinc) in blood samples of children having delayed language development without any obvious causes and to assess the relation between those metals and their toxic effect on language development.

PATIENTS & METHODS

The present study was conducted on 100 children presented to phonetic unit, Sohag University Hospitals. They were classified into two groups: group I (G1): 60 patients with delayed language development and group II (GII) as a control which included 40 children with normal language development who came with patients (the patients' relative in the same age).

Inclusion criteria:

Children aged two to six years who were diagnosed as delayed language development without obvious causes.

Exclusion criteria:

Children with perinatal problem, neonatal jaundice, epilepsy, autism, history of hearing impairment and brain damaged / motor handicapped children.

Ethical consideration:

According to the standard ethics drawn by the Faculty's Ethical Committee for Human Research. Written informed consent was discussed with the guardian of the children and obtained from all participants.

Both groups were subjected to the following protocol:

I-Elementary diagnostic procedures:

It included parent's interview, prenatal history, perinatal and postnatal history, milestones of the child, general examination, vocal tract examination, neurological examination and assessment of communicative abilities.

II. Clinical diagnostic aids:

Psychometric evaluation was done by Stanford Binet test (Lewis and Maud, 1972) and Vineland Social Maturity Scale (Doll, 1965). Assessment of language was done by Arabic Language Test (Kotby et al., 1995). Evaluation of peripheral hearing by tympanometry (which assess conductive hearing disorders) and pure tone audiometry (which assess sensorineural hearing disorders) was also done if needed as in cases of phonological error or family history of hearing loss.

III. Measurement of metals levels:

Three milliliters of blood were drawn from each child on heparinized tubes, The samples were mixed carefully by shaking. All the samples were stored in the refrigerator until analysis was done.

Extraction method:

Each sample was transferred into 100 ml conical flasks. Perchloric acid and nitric acid were added in a ratio 1: 3 as follows: 2 ml of perchloric acid (70% v/v) and 6 ml nitric acid (72% v/v). The conical flasks were covered with evaporating dish and the mixture was digested at low temperature, until a clear solution was obtained. The digest was made up to 20 ml with deionized water in a 20 ml standard flask (Rahman et al., 2006).

a) Detection method:

The level of metals (Cu, Pb, Cd, Mn,

and Zn) was assessed in the blood by using Inductively Coupled Plasma Mass Spectrometry (ICP-MS). Agilent 7500 ICP-MS present in faculty of Agriculture, Sohag University.

Statistical analysis:

It was done using SPSS 16.0 program for descriptive statistical analysis of data. The paired T test was used to compare between the normal and diseased cases. The correlation coefficient between the level of metal and the language development, mental and social IQ was determined.

RESULTS

The present study included 100 children. Group I comprised 60 children having delayed language development; 41 boys (68.3%) and 19 girls (31.7%). Group II (GII) included 40 kids; 26 boys (65%) and 14 girls (35%). The mean age of (GI) is 41.1 months and for (GII) is 40 months.No significant difference was found between both groups as regards the age (P = 0.980). No abnormality was detected in the studied cases by general examination and vocal tract examination. Also, tympanometry and pure tone audiometry were normal.

There was a significant statistical difference between both groups for motor development and language development as shown in table (1).

As regards social IQ, mental IQ, and language development for both external and internal, there was a highly significant difference between the diseased and the control groups as illustrated in table (2).

Table (1) : Motor and language development in the studied groups.

Group / Parameters	GI (Diseased)	GII (Control)	P value
	(Mean ± SD)		
Sitting age (months)	7.67±2.6	6.2±0.42	0.054*
Walking age (months)	16.8±6.5	11.9±0.73	0.021*
First word age (months)	20.8±8.2	11.9±0.73	0.015*
First sentence age (months)	32.8±11.1	23.6±1.09	0.039*

* Significant difference at P<0.05

Table (2) : Comparison between social IQ, mental IQ, and language development in the studied groups.

Group / Parameters	GI (Diseased)	GII (Control)	P value
	(Mean ± SD)		
Social IQ	78.97±9.4	97.8±1.89	0.000**
Mental IQ	68.7±13.1	93.6±2.66	0.000**
Internal language	21.3±9.9	39.6±11.55	0.001**
External language	18.5±9.2	39.6±11.55	0.001**

* Significant difference at P<0.05

The blood levels of copper, lead, cadmium, manganese and zinc in the diseased and control groups are shown in table (3). There was a significant statistical difference between both groups regarding just the level of lead where the mean value of the diseased group was 22.33 ± 1.27µg/dl as compared with the control group, 8.57 ±1.39µg/dl (P= 0.013).

Table (3) : Blood levels of copper, lead, cadmium, manganese and zinc (µg/dl) in the diseased and control groups.

Group / Metal	GI (Diseased)	GII (Control)	P value
	(Mean ± SD)		
Copper (µg/dl)	12.9 ± 0.47	10.8± 0.37	0.411
Lead (µg/dl)	22.33 ± 1.27	8.57 ±1.39	0.013*
Cadmium (µg/dl)	1.23± 0.14	0.62± 0.12	0.581
Manganese (µg/dl)	3.78 ± 1.27	2.16 ± 1.05	0.208
Zinc (µg/dl)	8.03 ± 0.67	7.29± 0.33	0.104

* Significant difference at P<0.05

The correlation between levels of studied metals and social, mental and language development is illustrated in table (4). There is only significant correlation between levels of lead and external language affection.

Table (4) : Correlation between different studied parameters and the level of metals.

Studied Parameters	Copper	Lead	Cadmium	Manganese	Zinc
	Correlation coefficient				
Social IQ	0.750	0.076	0.408	0.234	0.377
Mental IQ	0.566	0.344	0.407	0.773	0.406
Internal language	0.735	0.064	0.300	0.308	0.656
External language	0.607	0.034*	0.137	0.350	0.809

* Significant difference at P<0.05

DISCUSSION

There is a limited number of studies in our locality (Sohag governorate) regarding the effect of metals and delayed language development in early childhood. In the present work, the age of the studied children was preferred to be between two to six years as the Arabic language test used in the current study has specific objective measures for these ages. The levels of copper, lead, cadmium, manganese and zinc were measured in whole blood samples as the levels of metals in blood could be taken as representative of dose/exposure (Baldwin and Marshall, 1999).

In the present work, the levels of the studied metals are elevated in the diseased children. However, lead is the only metal which showed a statistically significant rise in the delayed language development group in comparison to the control group. The mean value of lead level in the diseased and healthy groups was 22.33 ± 1.27µg/dl 8.57 ±1.39 respectively (P= 0.013).

More or less similar, Samia et al. (2004) studied Pb blood levels in 164 children recruited from 2 different areas in Giza, Egypt. Those children were selected through a household-sampling frame specifically developed for this research. They found that 46% of rural children had blood Pb levels higher than 15 µg/dL, whereas only 20% of the urban children had levels exceeding 15 μg/dL. 55.8% of the studied children had Pb blood levels above the intervention level of 10 μg/dL adopted in the United States. The authors added that the Egyptian children's Pb blood levels were higher than those reported from several developed countries but were comparable to those reported from Saudi Arabia and Mexico. Egyptian children under the age of 5 years have the highest Pb blood levels because of increased gastrointestinal absorption and exposure through behaviors such as playing outdoors and increased hand-to-mouth activity.

The American Academy of Pediatrics (1993) stated that impairment of cognitive function begins to occur at lead levels greater than 10 μg/dL, even though clinical symptoms are not seen.The present findings are in agreement with many researches about autism. Blaurock-Busch et al. (2011) found a statistically significant difference in the mean hair levels of arsenic, cadmium, barium, cerium and lead by comparing the Autistic Spectrum Disorder (ASD) children to the control group. Yahya et al. (2013) conducted a study in Muscat to estimate the levels of eleven heavy metals and essential minerals in hair samples of children with ASD by inductively coupled plasma mass spectrometry. The results revealed that, children with ASD had significantly higher levels of all 11 analyzed heavy metals in their hair samples.

In contrast, Kern et al. (2007) reported that Pb was significantly lower in the hair of children with autism than in matched controls. On the other hand, Gahyva et al. (2008) found no significant correlation between the severity of language impairment and the concentration of lead for a group of 13 children presented with phonological and more than one language subsystem affection. Also, Yorbik et al. (2010) stated that there is no significant difference between Pb levels in the hair of children with autism and the normal group.

The primary target of lead toxicity is the central nervous system.The mechanism of lead induced toxicity is not fully understood. Rana (2008) stated that Pb intoxication can result in disruption of the function of various proteins and enzymes and disruption of certain cellular signaling processing in addition to generation of action potentials in certain nerve cells. Moreover, Nemsadze et al. (2009) reported that the prime targets to lead toxicity are the heme synthesis enzymes, thiol-containing antioxidants and enzymes (superoxide dismutase, catalase, glutathione peroxidase, glucose 6-phosphate dehydrogenase and antioxidant molecules like GSH). The low blood lead levels are sufficient to inhibit the activity of these enzymes and induce generation of reactive oxygen species.

Blaurock-Busch et al. (2012) showed greatest improvements for verbal and nonverbal communication of autism with using of 2,3-dimercaptosuccinic acid (DMSA) challenge test. Oral chelator (DMSA) was used to mobilize heavy metals from extra vascular pools in children with autistic spectrum disorders (ASD).

The present work showed elevated level of Cd in the diseased group, where the mean value was 1.23± 0.14μg/dL and that of the control group was 0.62 ± 0.12 μg/dL.

The results of the present work are in agreement with those reported by Capel et al. (1981) & Marlowe et al. (1983) where higher concentrations of hair Cd were reported in children with mental retardation and learning difficulties or dyslexia. Also, Monroe and Halvorsen (2006) and Cao et al. (2009) recorded that exposure to Cd severely affects the function of the nervous system, with symptoms including headache and vertigo, olfactory dysfunction, parkinsonian-like symptoms, peripheral neuropathy, decreased equilibrium, decreased ability to concentrate, and learning disabilities. Cadmium expresses its neurotoxic effects by induction of neuron cell apoptosis and reactive oxygen species (Bo and Yanli, 2013).

Copper is an essential element in mammalian nutrition as a component of metalloenzymes. Both copper deficiency and copper excess produce adverse health effects (Stern et al.,2007). As regards the levels of Cu in our study, the delayed language development group showed higher concentrations (12.9 ± 0.47μg/dL) than the healthy one (10.8± 0.37 μg/dL). The present results are in agreement with findings reported by Russo (2011), where the autistic individuals had significantly elevated levels of copper and elevated Cu/Zn (Copper Zinc ratio).

The level of zinc in the diseased group was higher (8.03 ± 0.67 μg/dL) than the control group (7.29± 0.33 μg/dL). Contradictory to these results, Russo and Devit (2011) found lower zinc level in the diseased subjects with Autism than the normal matched controls. On the other hand, Russo et al. (2012) stated that there was a correlation between Cu/Zn and expressive language, receptive language, focus attention, hyperactivity, fine motor skills, gross motor skills and Tip Toeing. There was a negative correlation between plasma zinc concentration and hyperactivity, and fine motor skills severity in autistic children.

Manganese (Mn) is an essential nutrient, involved in the metabolism of amino acids, proteins, and lipids, but in excess, can be a potent neurotoxicant (Riojas-

Rodriguez et al., 2010). Saric (1986) recorded that normal whole blood levels of Mn range from 7-12 µg/L. Mergler et al. (1999) stated that blood levels as low as 7.5 µg/l can be associated with neurological dysfunction.

The present work showed higher level of manganese (3.78 ± 1.27 µg/dl) in the delayed language development group than the control group (2.16 ± 1.05 µg/dl). These findings are in agreement with those recorded by Riojas-Rodriguez et al. (2010) where they proved that elevated level of manganese in blood (9.5 µg/L) was inversely associated with intellectual function in young school-age children (Total and Verbal IQ score). Similarly, Khalid et al. (2012) reported that drinking water containing manganese is a potential threat to children's health due to its associations with a wide range of outcomes including cognitive, behavioral and neuropsychological effects.

In contrast, Malarveni and Arumugam (2012) stated that a significant decrease in the concentration of Mn was observed in the hair and nails samples of autistic subjects.

Conclusion and recommendations:

It can be concluded that lead in childhood might affect the language development in addition to the development of other body activities such as sitting, walking and talking.

It is recommended to screen blood lead levels in early childhood. A bigger sample size is needed to investigate the effect of metals on language development. Follow up and early management of those cases with potentially harmful levels and are needed to avoid language disorders in children.

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التأثير السام لبعض المعادن على النمو اللغوى فى عينة من الأطفال فى محافظة سوهاج

المشتركون فى البحث

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من قسم الطب الشرعى والسموم الإكلينيكية - *قسم الأنف الأذن والحنجرة - وحدة التخاطب - جامعة سوهاج

التعرض المزمن للمعادن له تأثير سام خفى على الجهاز العصبي في مرحلة الطفولة المبكرة. فقد يسبب اضطرابا فى النمو اللغوى والتعلم. ويهدف هذا البحث الى تقدير مستوى بعض المعادن (النحاس والرصاص والكادميوم والمنجنيز والزنك) في عينات من دم الأطفال اللذين يعانون من تأخر فى النمو اللغوى دون أي أسباب واضحة وتقييم العلاقة بين مستوى هذه المعادن وتأثيرها السام على النمو اللغوى. وقد أجريت هذه الدراسة على ٦٠ طفلا يعانون من اضطراب فى النمو اللغوى و ٤٠ حالة من الاطفال الاصحاء (كمجموعة ضابطة). تم أخذ التاريخ المرضى واجراء فحص عام و فحص لمنطقة الأحبال الصوتية وفحص الجهاز العصبي لكل الحالات. وتم تقييم الأطفال اكلينيكيا باجراء عدة اختبارات لتقدير مستوى الذكاء العقلى و الاجتماعى والمهارات الذهنية الاخري وأيضا اختبار اللغة العربية. وتم التأكد من سلامة السمع باستخدام جهاز فحص طبلة الأذن (tympanometry) وجهاز قياس سمع النغمة النقية (pure tone audiometry) . كما تم تقديرمستوى النحاس ، الرصاص، الكادميوم ، المنجنيز والزنك فى دم الاطفال باستخدام جهاز Inductively Coupled Plasma Mass Spectrometry (ICP-MS) (الاسبكتروميتر الكتلى- بلازما الحث المزدوج).

وقد تبين أن مجموعة الأطفال المريضة تعانى تأخرا في النمو اللغوى ذو دلالة احصائية ، وكذلك مستوي الذكاء ونمو أنشطة الجسم الأخرى مثل الجلوس والمشي والكلام. كما أظهرت الدراسة ارتفاعا فى مستوي المعادن المختبرة فى دم الاطفال المريضة (على الأخص الرصاص) مقارنة بالمجموعة الضابطة. وأسفرت الدراسة عن ارتفاع ذو دلالة احصائية فى متوسط قيم الرصاص فى المجموعة المريضة مقارنة بالمجموعة الضابطة وكانت (٢٢,٣٣ ± ١,٢٧ ميكروجرام / ديسيلتر و٨,٥٧ ± ١,٣٩ ميكروجرام / ديسيلتر على التوالي). ونخلص من هذا إلى أن ارتفاع مستوى بعض المعادن في فترة الطفولة المبكرة قد يؤثر على النمو اللغوى بالإضافة إلى تأثيره على نمو أنشطة الجسم الاخرى. لذلك ينصح بقياس مستوي المعادن في دم الأطفال في مرحلة الطفولة المبكرة ومحاولة علاج تلك الحالات التى تعانى من ارتفاع فى نسب هذه المعادن ومتابعتهم عن طريق الفحص الإكلينيكى والمعملى لتجنب تأخر النمو اللغوى .