REPORT

Central nervous system (CNS) toxicity caused by metal poisoning: *Brain as a target organ*

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Abstract: People relate the neural disorders with either inheritance or psychological violence but there might be some other reasons responsible for the ailment of people that do not have such a background. The present study explains the chronic effect of heavy toxic metals on nervous system. During experimentation, rabbits used as laboratory animals, were given test metals in their diet. Concentration of metals given to them in the diet was less than their tolerable dietary intake. Behavioral changes were observed during experimentation. Periodic increase in the metal concentration was seen in the blood sample of rabbits. They were slaughtered after a period of eight months of slow poisoning. Histological examination of brain tissues was performed. The brain samples were analyzed by Atomic absorption spectroscopy and Inductively Coupled Plasma Mass Spectrometry to find the retention of heavy metals in mammalian brain. Concentration of lead, mercury and cadmium in the blood samples of occupationally exposed people and patients with neurological disorders at the time of neurosurgery was determined by using the same techniques. During circulation, toxic metals passes through the nerve capillaries to settle down in the brain. Heavy metals cross the blood brain barrier and 'may retain themselves in it. Brain tumors and biopsy samples of patients with neurological disorder were also analyzed to relate neurotoxicity and heavy metal poisoning. Results obtained shows that lead, mercury and cadmium retain themselves in the brain for longer period of time and are one of the causes of neurotoxicity.

Keywords: Heavy metals, metal toxicity, brain target organ, metal poisoning, blood brain barrier.

INTRODUCTION

A toxic metal may, at times be responsible for permanent disorders or malfunctioning of organ systems leading finally to death (Timbrell 1995). Heavy metal poisoning has become an increasingly major health problem, especially since the industrial revolution, effect may be either acute or chronic (Mahajan, 1990; Fournier *et al.*, 1998).

Nearly all organ systems are involved in heavy metal toxicity; however, the most commonly involved systems include the (central nervous system) CNS, (peripheral nervous system) PNS, hematopoietic, renal, and cardiovascular. The other problems include carcinogeni city, nephrotoxicity, nervous system toxicity, respiratory system toxicity, endocrine and reproductive effects.

The brain as a target organ

Brain is a target organ for some toxins. Heavy metals compromises normal brain development and neurotransmitter function. Toxic metals such as lead *is neurotoxic* (Bartolome *et al.*, 1999) which concurrently with prenatal or neonatal developmental insults, dietary deficits and stress damage the brain structures and down regulate essential neurotransmitters, because toxic metals are retained in bone urine, feces and astroglial cells in the brain (Dupler *et al.* 2001; Group 1998). Small amounts of toxic metals appear in hair, nails, sweat, saliva and breast milk (Canfield *et al.* 2003; Oheme *et al.*, 1972). Uptake during fetal development and early childhood has long lasting effects on development and behavior. Although ligand formation is the basis for much of the transport of heavy metals throughout the body, some metals may compete with ionized species such as calcium and zinc to move through membrane channels in the free ionic form. For example, lead follows calcium pathways in the body (Clayman *et al.*, 1989; O'Brien *et al.*, 2001; Brangstrup Hanse *et al.*, 1981).

Mercury, a widespread environmental contaminant (Done *et al.*, 1980), has no known biological function and is highly toxic in all its forms to the human health (Huel *et al.*, 1981). The fetal brain is more susceptible to mercury-induced damage than that of an adult (Huel *et al.*, 1984). Mercury toxicity (Jordau *et al.*, 1929) often presents with CNS dysfunction (e.g., erethism). Chronic exposure may lead to an intention tremor the most consistent

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neurological finding in chronic toxicity. The CNS affects are slowing or incompletely reversible. In chronic intoxication there is "mercury line" at the gingival border similar to the "lead line", death may sometimes occur. Neurotoxicity may also occur with symptoms such as tremors, emotional liability, headaches and polyneuropathy (Louis, Chang, 1977).

Cadmium causes nerve or brain damage (Cherry *et al.,* 1981). Long-term exposure to cadmium leads to selective accumulation in the liver and renal cortex, such that up to 75% of the total body burden is found in these organs (Friberg *et al.,* 1985). Lower concentrations are found in brain, bone, and fat (Sorensen *et al.,* 2005).

Workers exposed to cadmium showed increased frequencies of subjective symptoms such as fatigue, headache, and sleep disturbances, disturbances of sensory and motor functions, anorexia, and Insomnia (Leret, 2003). Lead and cadmium levels tend to have positive correlations with each other. These two metals have been found to have different mechanisms of CNS damage, with cadmium affecting verbal ability more and lead affecting performance measure.

MATERIALS AND METHODS

Patients suffering from different neurological disorders were studied by collecting their blood samples, cotton swabs of blood during neurosurgery and some samples of tumor tissues from biopsy samples. Rabbits were used as laboratory animals. They were given test metals in their diet. Lead, mercury and cadmium are chosen because of their neurotoxicity, frequency of occurrence at hazardous waste sites, and involvement in environmental contamination. Their blood samples were analyzed periodically. Finally animals were slaughtered and samples of their brain tissues along with their blood samples were analyzed by Atomic absorption (Perkin-Elmer 3110 & Varian Spectra AA125), and ICP MS (Plasma argon: 1.5L/min RF Power: 1300Watts, Nebulizer: 0.8 ml/min) are used for the analysis of trace metals.

Sample Preparation

Digestion of Samples

Samples (Brain & Blood) were weighed and digested with 10 ml of 16 N HNO_3 then another 5ml of 16 N HNOs was added to form a slurry so that the sample is converted into metal ions. After cooling to room temperature, the digested solutions were diluted to 100ml with deionized water for analysis.

Retention of heavy metals in the brain grouping of rabbits

In order to find the retention of heavy metal in the soft tissues of brain, rabbits were used as experimental materials. 8 rabbits (A, B, C, D, E, F, G & H) were grouped in 4 (two rabbits in each group)

Rabbits A and B are marked in group 1
Rabbits C and D are marked in group 2
Rabbits E and F are marked in group 3
Rabbits G and H are marked in group 4

Control reading of their blood sample was taken. They were kept separated at the time of feeding so as to obtain better results and were observed for a period of eight months.

Dietary intake of rabbit's groups

Rabbits were fed with the salts of heavy metals (lead, mercury and cadmium) in their diet. Concentration of metals added in the diet was adjusted according to their body weights and was less than the tolerable toxic metal limits. Toxic metal contaminated food was given to them twice a week

Group 1 was fed with the lead-contaminated diet
Group 2 was fed with the mercury-contaminated diet
Group 3 was fed with the cadmium-contaminated diet
Group 4 was taken as a controlled group

Changes observed in test rabbits during experimentation

Changes were observed during experimentation regarding their behavior, locomotors activity (measured by regular monetring), body weight, dietary intake and hair loss.

Blood samples of rabbits

Metal concentration in the blood samples of rabbits were determined periodically. Animals were slaughtered after a period of eight months of slow metal poisoning. Rabbit E (rabbit fed on mercury contaminated diet) died during experimentation before slaughtering, imediately samples of blood and brain tissues of Rabbit E were collected.

Histological examination of brain tissues of slaughtered rabbits

The brain tissues were examined. Histological examination of brain tissues of slaughtered rabbits was performed in comparison to brain tissues of control group

Brain sample analysis

Brain samples were analyzed to find the retention of heavy metals in mammalian brain. Samples were digested and solutions were running through Atomic Absorption spectrophotometer and ICPMS for metal analysis.

Analysis of blood samples of patients occupationally exposed to toxic metals

Blood samples of occupationally exposed people i.e. rickshaw driver, traffic policeman, industrial worker, chain smoker were analyzed.

Patient 1

This patient was 33 years old male, found to be suffering from lead Toxicity. This patient was a rickshaw driver and

was living in most polluted area (Badami Bagh), Lahore Pakistan. He was likely exposed to lead pollution throughout the day. This patient had complains of hypertension and depression.

Patient 2

This patient was 41 years traffic Policeman, found to be suffering from Lead Toxicity. He was posted at Mazang Chungi Lahore Pakistan. This person had the problem of aggressiveness in his behavior (His neuro consultant's report, Physiologist's comments)

Patient 3

The patient under observation was 7 years old, suffering from Lead Toxicity, he was working in workshop in Balal Gunj (Cars spare parts market) Lahore Pakistan and also living there from childhood. The place was largely congested by old heavy machinery and therefore there was direct or indirect contamination. Inhalation of tetra ethyl lead and other lead compounds were also very common. This patient had complaints of headache and depression.

Patient 4

This patient was a 52 years old dentist exposed to mercury vapors and occupationally had sever headache.

Patient 5

This patient was 35-year-old male, working 'in paper manufacturing factory at Shaikhupura road (heavy traffic dusty area). He was occupationally exposed to mercury vapor during wood pulp treatment, gradually he became hyperactive (According to the relevant doctor).

Patient 6

This patient was 55-year-old male, found to be suffering from mercury toxicity according to his blood test report. Professionally this patient was a farmer living in industrial area of Kalashakako, near Lahore. Biological and food samples of this patient were found to contain to contain high concentrations of mercury. This patient suffered from dental pain about four years ago and was treated by amalgam filling that leaked out one and a half year back. He was suffering from inflammation of gums, loosening of teeth, indigestion and headache.

Patient 7

This patient was 43 years old male suffering from lung cancer and mental disturbances. Professionally this patient was welder living in Badami-Bagh area (Thickly Populated highly polluted) of Lahore. This area has small industries and effluent of these industries discharge into atmosphere without any treatment Moreover, the patient was a regular smoker.

Patient 8

This patient was 22 years old young man working in paan (Betel leaf) and cigarette shop. He was a non-smoker but the tobacco smoking contaminates the atmosphere. The area of the patient was situated at General Bus Stand and exhaust released from various public automobiles that made the environment polluted. He was found hypertensive by regular monitoring of his Blood Pressure.

Patient 9

This patient was 37 years rickshaw driver and habitual of using tobacco cigarettes. He had to become a part of contaminated environmental web throughout the day. He was suffering with Kidney disorder.

Section 2

Sample preparation and analysis

All samples were digested as discussed earlier. The samples were analyzed by Atomic Absorption Perkin-Elmer 3110. Determination of all metals in samples were analyzed by AAS with analytical conditions given in tables for specific metals as follows, Analytical conditions for lead, mercury and cadmium is given in table 1

Section 3

Metal concentration throughout the body

The concentration of metals was same in the blood throughout the body. In order to confirm this, blood samples of the patients with neurological disorders were analyzed. Patients had neurosurgery at children hospital, Lahore (case 1) and General Hospital (Case 2). Clean cotton plugs which have been used by the neurosurgeons during neurosurgery were weighed. The used cotton plugs containing blood sample of the patient were analyzed analyzed. The blood content was calculated by subtracting the weight of the cotton plug before use.

Case *1*

Patient's history

Sex: Male

Age: 14 years

Relevant Clinical Data were from Hospital Record (Ali Children Hospital Lahore) Problems Left frontal enhancing tumor. Neoplastic brown and dark brown mass Histopathological examination of the section revealed appearance of the glaucoma with features of a highly vascular low-grade astrocytoma, with dilated blood vessels in some areas. There is no nuclear pleomorphism and no mitotic activity. The features are consistent with grade 2 astrocytoma.

Case 2

Patient's history

Sex: Female

Age: 25 yrs

Relevant Clinical Data obtained from Hospital Record (General Hospital Lahore). Problem Pearly yellow white tumor removed piecemeal

Sample preparation and analysis

Cotton plug sample were digested by the already discussed method. Cotton plugs were weighed before and

Table 1: Analytical Conditions for Cd, Pb and Hg

Element and measurement wavelength	Cd 228.8 nm	Pb 283.3 nm	Hg 253.6 nm
Hollow cathode lamp current	5 mA	10 mA	4 mA
Slit Width	1.9 A	5-20 ug cm-3	1.9 A
Burner height	5 mm	3.8 A	100-400 ugcm^{-3}
Auxiliary gas flow rate	Air 10 Lit/min	Average 1	3.8 A
Fuel gas flow rate	C_2 H_2 2.4 Lit/min	air 10 L / min	Check 1
Measurement Mode	HCl	C_2H_2 2.3 L / min	x5

after their use in neurosurgery. Amount of blood absorbed in the cotton plugs was calculated. Analysis was done by Atomic Absorption Spectrometry.

Section 4

Determination of heavy metals in the human brain tumors

All the samples were collected from Gulab Devi Hospital's Pathology Lab and relevant Clinical Data obtained from Hospital Record.

Case 1

Patient's History
Sex: Male
Age: 60 years
Headache and left hemiplegia, C.T. Scan revealed left parietal SOL, Left parietal craniotomy was done. A well circumscribed mass, gray white firm at periphery and soft in the centre, relatively a vascular, containing thiombosed vessels removed gross totally.

Case 2

Patient's History
Sex: Male
Age: 50 years
Headache, vomiting and fits.
Right parietal craniotomy and excision of meningioma Red gray, soft to firm in consistence, attached to dura, arising from petrous bone.

Case 3

Patient's History
Sex: Female
Age: 32 yrs
Highly vascular tumor, piecemeal removal, friable to firm in consistence, gray white.

Case 4

Patient's History
Sex: Female
Age: 22 years
Right frontal tumor
Craniotomy was done
Gray white, firm, moderately vascular Tumor found.

Case5

Patient's History
Sex: Male
Age: 24 years
Trochlear Schwan nome
The specimen was taken from C-P angle which is gray white, moderately vascular, firm and calcified tumor.

Case 6

Patient's History
Sex: Female
Age: 42 years
Relevant Clinical Data obtained from Hospital Record:
Rt tinnitus, Deafness, Headache
On Examination: Right sided facial palsy, right sided numbness, Ataxia, cerebellar signs positive.
Preoperative gray yellow Cerebral Palsy angle mass, pushing through nerves. Moderately vascular, encapsulated adherent to brain.

Sample preparation

3gm of affected region of brain, removed during neurosurgery was digested with concentrated Nitric acid and were converted to clear solution with deionized water finally analyzed, by ICP-MS (Plasma argon: 1.5L/min RF Power: 1300Watts, Nebulizer: 0.8ml/min).

RESULTS

The following results were collected from samples of control mammals (lab Rabbits), Blood Samples of patients with neurological disorders, brain tumor samples, cotton swabs collected during neurosurgeries.

Allowable concentration of heavy metals in blood and urine

Allowable concentration of Heavy Metals in Blood is given in table 2

Results of metal concentrations analysis in brain samples of rabbits

Dietary intake of Rabbits is given in table 3, and Concentration of heavy metals in the brain samples of injected Rabbits heavy metals dose is given in table 4

Results of metal concentration throughout the body

i) Blood sample analysis of occupationally exposed patients with neurotoxicity

Metal concentrations in blood Sample of Occupationally toxic metal Exposed Patients were analyzed for metal concentration by Atomic Absorption Spectroscopy. Results are shown in table 5.

Table 2: Allowable concentration of Heavy Metals in human Blood (Clarkson, *et al*)

Metals	Conc. in Blood
Pb	0.3 to 0.4 ppm
Hg	0.036 ppm
Cd	0.003 ppm

ii) Concentration of metals in blood samples taken directly from brain

Metal concentrations in blood samples directly collected from the brains by extracting cotton swabs used during Brain operations were also analyzed and results are given in table 6

Results of human brain tumors

Metal concentrations in Biopsy samples of brain tumors collected during Brain operations were also analyzed and results are given in table 7

DISCUSSION

Experimental rabbits with high levels of toxic metals showed aggressiveness and hyperactivity. No significant

Table 3: Dietary intake of rabbits

Group	Metal given	Rabbits	Weight of rabbits before experimentation (kg)	Zero reading of blood sample before experimentation	Dietary intake of rabbits ((µg/day)
1	Pb	A	2	BDL	10 µg (twice a week)
		B	2.5	BDL	(0.001 ppm)
2	Hg	C	1.8	BDL	5) µg (twice a week)
		D	2.0	BDL	(0.0005 ppm)
3	Cd	E	2.25	0.2	10. µg (twice a week)
		F	1.9	BDL*	(0.001 ppm)
4	Control	G	2.0	BDL *	Normal diet
		H	2.25	BDL *	

*Below Detection Limit

Table 4: Concentration of heavy metals in the brain samples of rabbits with injected heavy metals (Analyzed by ICP-MS)

Group No.	Rabbits	Metals given	Tolerable dietary intake µg/day	Dietary intakes of rabbits	Weight of brain samples (g)	Concentration of injected metal in the brain (µg)
1	A	Pb	90	10µg (twice a week)	5.003	189
	B	Pb	90	10µg (twice a week)	6.2	156
2	C	Hg	5.2	5µg (twice a week)	5.3	61
	D	Hg	5.2	5µg (twice a week)	5.8	59
3.	E	Cd	47-62	10µg (twice a week)	7.511	312.5
	F	Cd	47-62	10µg (twice a week)	5.26	100
4	G	None			6.0	Nil
	H	none			5.34	Nil

Table 5: Results of Blood Sample Analysis of Occupationally Toxic metal Exposed Patient

Patient #	Age/Sex	Problem	Metal	Conc. in	Blood (ppm)
			Pb (0.3 to 0.4)	Hg (0.036)	Cd (0.003)
1	337 Male	Hypertension & depression	0.89 (excessive)	0.03	0.041 (excessive)
2	41/ Male	Aggressive behavior	0.65 (excessive)	0.03	0.01 (excessive) •
3	*11* Male	Headache & depression	0.71 (excessive)	0.03	0.01 (excessive)
4	527 Male (dentist)	Headache & Bleeding Gums	0.37	0.1 (excessive)	0.003
5	357 Male	Hyperactivity	0.46 (excessive)	0.17 (excessive)	0.035 (excessive)
6	557 Male	Inflammation of Gums, Indigestion & headache	0.53 (excessive)	0.091 (excessive)	0.001
7	437 Male (Chain Smoker)	Lungs Cancer & Mental disturbance	0.46 (excessive)	0.08 (excessive)	0.035 (excessive)
8	227 Male	Hypertension	0.59 (excessive)	0.41 (excessive)	0.006 (excessive)
9	377 Male	Kidney disorder (Doctor's Report)	0.01	0.38 (excessive)	0.01 (excessive)

difference was found between experimental and control groups in locomotors activity measured by regular observation in first two months. Later on, rabbits fed with lead and cadmium became sluggish. Appreciable influence on body weight and food intake was observed. Hair loss was seen in the rabbits fed with food containing cadmium and mercury. Long-term exposure to cadmium leads to selective accumulation in the liver and renal cortex, brain, bone, and fat.

Histological examination of brain tissues of slaughtered rabbits in comparison to controlled groups showed that mercury and cadmium damage the brain tissues.

Results of the present study reveal that persons exposed to cadmium showed increased frequencies of subjective symptoms such as fatigue, headache, and sleep disturbances, disturbances of sensory and motor functions, anorexia, and anosmia (the loss of the sense of smell). Patients suffering from cadmium poisoning have all the symptoms related with Cadmium toxicity, like headache, mental disturbance and hypertension. All the patients exposed to lead showed all the symptoms expected in lead poisoning. They were found suffering from hypertension (monitored regularly), headache, depression and aggressiveness.

The results of analysis were almost same in the blood samples collected from the body and from the cotton swabs collected during neurosurgeries. This shows that the concentration of metals in the blood is same throughout the body. During circulation, it passes through the nerve capillaries to bath the brain. Heavy metals cross the blood brain barrier and may retain themselves in it.

Table 6: Concentration of metals in blood samples taken directly from brain (Cotton swabs collected during brain operations)

Case No.	Patient' s history	Operative findings from the hospital record	Metals determined	Conc. of metals in blood (ppm)	Conc. of metals in blood absorbed by the cotton plugs used in neurosurgery (ppm)
1	Female Age: 25 years	Pearly yellow white tumor removed piecemeal	Pb	0.73	0.75
			Hg	0.059[1]	0.062
			Cd	0.67	0.69
2	Male Age 14 years	Left frontal enhancing tumor	Pb	0.41	0.40
			Hg	0.02	0.023
			Cd	0.01	0.01

Table 7: Concentration of heavy metals in the human brain tumor sample

Case No.	Weight of brain tumor removed (g)	Metals analyzed	Metals concentration in 1g of tumor samples (µg)	Metal concentration in total amount of brain tumor (µg)
1	47	Pb	0.43	20.21
		Hg	0.103	4.841
		Cd	0.38	17.86
2	54	Pb	0.58	31.32
		Hg	0.20	10.8
		Cd	0.06	3.24
3	6	Pb	0.71	4.26
		Hg	NIL	NIL
		Cd	NIL	NIL
4	3.5	Pb	0.14	0.49
		Hg	0.09	0.315
		Cd	0.17	0.595
5	23	Pb	NIL	NIL
		Hg	0.14	3.22
		Cd	2.06	47.38
6	7.5g	Pb	0.62	4.65
		Hg	0.28	2.1
		Cd	2.3	17.25

Concentration of heavy metals in the brain tumor samples shows that heavy toxic metals (lead, mercury and cadmium) can also be retained in the human brain. They can become a part of soft brain tissues of the body and may be considered as one of the causes of neurotoxin diseases such as severe headache, fits, depression, and anxiety.

CONCLUSION

The present study develops a relationship between neural disorders and heavy metal toxicology, to develop awareness. Accumulation of heavy metals in the soft tissues of rabbit's brain suggests that these metals become a part of brain tissues and remain there for a longer period. Results of blood analysis of occupationally exposed people show that exposure to environment is responsible for neural diseases. Blood containing increased amounts of heavy metals then normal bathes different parts of body during circulation, and passes the blood brain barrier. The metal concentration in the blood passing the blood brain barrier is same as shown by the results of blood samples obtained directly from the brain at the time of neurosurgeries. It is also observed from the results of tumor samples that heavy toxic metals (lead, mercury and cadmium) can also be retained in the human brain. They may retain themselves in the soft brain tissues and considered as a cause of neurological disorders. The people who are affected by metal toxicity are suffering from depression, headache, fits, anxiety, mental disorders and irritability in their behavior.

Retention of all three metals resulted in mammalian brain. Heavy Metal Toxicity is one of the causes of CNS disorders. Avoiding heavy metal exposure is impossible, but we can take steps to understand this threat and put into action policies of prevention and treatment that may help to lessen the negative impact that these agents have on human health.

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