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BLOOD LEAD LEVELS IN PRIMARY HYPERTENSION

DISSERTATION SUBMITTED FOR M.D. DEGREE BRANCH 1

(GENERALMEDICINE)

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CERTIFICATE

This is to certify that the dissertation entitled **"*BLOOD LEAD LEVELS IN PRIMARY HYPERTENSION*"** submitted by ***Dr. S. VIDYA*,** to the Faculty of Medicine, The Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D. Degree Branch I (General Medicine) is a bonafide research work carried out by her under our direct supervision and guidance.

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DECLARATION

I Dr.S.Vidya, solemnly declare that the dissertation work entitled **"*BLOOD LEAD LEVELS IN PRIMARY HYPERTENSION*"** has been carried out by me. It was not submitted to the award of any degree / diploma to any university either in part or in full form previously.

This is submitted to the The Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the regulation for the award of M.D. Degree Branch I (General Medicine).

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INTRODUCTION

Cardiovascular disease is an epidemic of modern society. Hypertension is one of the most common forms of cardiovascular disease the prevalence of which increases with age. It is one of the most important public health problems and if left untreated can lead to serious morbidity and mortality from cardiac, cerebrovascular and renal diseases.

Metals constitute a major category of toxins that pose a significant threat to health through occupational as well as environmental exposures. One indication of their importance relative to other potential hazards is their ranking by the U.S Agency for Toxic Substances and Diseases Registry, which lists all hazards present in toxic waste sites according to their prevalence and the severity of their toxicity. The first, second, third and sixth hazards on the list are heavy metals; lead, mercury, arsenic and cadmium respectively (Howard Hu et.al 2001.).

Lead was probably one of the first metals to be produced by man being known since 3500 B.C., in agreement with archaeological discoveries done in Egypt. Lead poisoning is as ancient as Roman history. A strong association between blood lead level and the prevalence of hypertension was noted in the second National Health and Nutrition Examination Survey (NHANES II) conducted during 1976 and 1980 (Vupputuri et al 2003). Several clinical and

laboratory observations are consistent with the hypothesis that high lead levels may be important in the development of primary hypertension in humans. Bagchi et al (2005) has demonstrated that elevated lead levels was associated with an increase in systolic BP in rats.

The interest in blood lead levels as a potential risk factor for cardiovascular disease has ballooned in the last several years with numerous abstracts and research papers, multiple editorials, review articles being published regarding this issue.

While some animal studies have found a positive association between blood lead levels and hypertension some others have come to an opposite conclusion (Shelkovnikov et al 2001). Thus the role of blood lead levels as a risk factor for systemic hypertension remains controversial and further studies regarding the pathogenesis of lead induced hypertension are needed.

Similarly some human studies have found no correlation between blood lead levels and hypertension [Cheng et al 2001]. Instead they found correlation between bone lead levels (a more sensitive marker for chronic low grade lead exposure) and hypertension.

Hence an attempt has been made here to study the prevalence of elevated blood lead levels in patients with primary hypertension and its correlation with hypertensive target organ damage.

AIMS AND OBJECTIVES

1. To measure blood lead levels in patients with primary hypertension.

2. To identify whether any association exists between age, sex and target organ damage and the presence of elevated blood lead levels.

3. To correlate the results with standard data available.

REVIEW OF LITERATURE

HYPERTENSION

An elevated arterial pressure is one of the most important public health

problems and despite its widely recognized high prevalence and associated danger, it remains inadequately treated in majority of the patients. It is common, readily detectable, and usually easily treatable and if left untreated can lead to serious morbidity and mortality from cardiac, cerbrovascular, vascular and renal disease. Adequate hypertension control remains elusive because of the asymptomatic nature of the disease for the first 15-20 years even as it progressively damages the cardiovascular system (Kaplan, 1998). Although our understanding of the pathophysiology of hypertension has increased in 90% to 95% of cases, etiology is still mostly unknown.

Definition and Classification:

Blood pressure is distributed in a typical bell shaped curve within the overall population. As seen in the Multiple Risk Factor Intervention Trial (MRFIT), the long-term risks for cardiovascular mortality rise progressively over the entire range of blood pressure, with no threshold that clearly identifies the potential danger. Therefore the definition of hypertension is somewhat arbitrary and usually taken as that level of pressure associated with doubling of long term risks. As per JNC-7 report Hypertension is defined as systolic B.P $\geq$ 140mm Hg and or diastolic B.P $\geq$ 90mm Hg. The JNC classification is shown in table 1.

Table 1

Category	Systolic B.P. (mm of Hg)	Diastolic BP (mm of Hg)

Normal	<120	and	<80
Pre-Hypertension	120-139	Or	80-89
Hypertension Stage 1 Stage 2	 140-159 >160	 Or Or	 90-99 >100

Prevalence:

The prevalence of hypertension depends on both the racial composition of the population studied and the criteria used to define the condition. In a white sub-urban population like that in the Framingham Study, almost one half have blood pressure greater than 140/90 mm Hg. In India as per study conducted by Gupta et al in 1977-78, the prevalence was 59.9 and 69.9 per 1000 in males and females respectively in urban population and 35.5 and 35.9 per 1000 in males and females respectively in rural population.

More than 90% of all hypertensives will have no recognizable cause.

The prevalence of various secondary causes of hypertension is shown in Table -2 (Rudnick et al)

Table -2

Diagnosis	Percentage
Essential Hypertension	94%
Chronic renal disease	5%

Reno-vascular disease	0.2%
Coarctation of aorta	0.2%
Primary aldosteronism	0.2%
Pheochromocytoma	0.2%
OCP-induced hypertension	0.2%

Natural history and Complications:

The pathological hallmark of uncontrolled hypertension is acceleration of atherosclerosis. The higher the BP, the more likely that various cardiovascular disease will develop prematurely. If untreated, 50% of hypertensive patients die of coronary artery disease or congestive cardiac failure, about 33% of stroke and 10-15% of renal failure. A meta-analysis of nine major prospective studies shows a direct continuous and apparently independent association of diastolic BP with both coronary artery disease and stroke (MacMohan et al, 1990). The various target organ damage due to hypertension is as follows.

Table 3

Target Organ Damage

Heart

Left ventricular hypertrophy

Angina or myocardial infarction

Heart failure

Brain

Stroke or transient ischemic attack

Chronic kidney disease

Peripheral arterial disease

Retinopathy

Overall Cardiovascular Risk:

The degree of risk from hypertension can be categorized with reasonable accuracy by taking into account

1. The level of Blood Pressure
2. The presence of target organ damage.
3. The co-existence of other cardiovascular risk factors. (Jackson, et al 1993)

The goal of anti-hypertensive therapy should not only be reduction of blood pressure but also treatment of other risk factors. The major cardiovascular risk factors indicated in JNC -7 report are:

1. Hypertension
2. Cigarette smoking
3. Obesity
4. Physical inactivity
5. Dyslipidemia
6. Diabetes mellitus
7. Microalbuminuria or estimated GFR <60 ml /min
8. Age (>55 for men, >65 for women)
9. Family history of premature cardiovascular disease (<55 for men, <65 for women)

Mechanisms of Primary Hypertension:

No single or specific cause is known for most hypertension and the condition is referred to as primary in preference to essential. Blood Pressure is the product of cardiac output and peripheral vascular resistance (BP = CO × PVR) and increase in blood pressure develops in response to factors which affects these two forces. The development of the disease is slow and gradual.

Genetic Predisposition:

In studies of twins and family members in which the degree of familial aggregation of blood pressure level is compared with closeness of genetic sharing, the genetic contributions have been estimated to range from 30% - 60%

(Harrap,1994). Unquestionably environment plays some role and Harrap (1994) offers an interaction between genes and environment as a working model in which the average population pressure is determined by environment but the blood pressure rank within the distribution is decided by genes. Genetic abnormalities may be monogenic as in Liddle syndrome, glucocoriticoid remediable aldosteronism and apparent mineralocorticoid excess (Luft, 1998) or involves polymorphism of genes involving Renin Angiotension System (Staessen et al, 1999), Aldosterone system or adrenergic receptors.

Fetal Environment:

Low birth weight as a consequence of fetal under nutrition is followed by an increased incidence of high blood pressure later in life (Law and Shiell, 1996). Brenner and Cherton hypothesized that a decreased number of nephrons from the intrauterine growth retardation could very well serve as a permanent irreparable defect that eventuates in hypertension (Brenner and Cherton, 1996)

Renal Retention and Excess of Dietary Sodium:

A considerable amount of circumstantial evidence supports a role for sodium in the genesis of hypertension. To induce hypertension some of that excess sodium must be retained by the kidneys. Such retention could arise in a number of ways.

- A decrease in the filtration surface by a congenital or acquired deficiency in nephron number or function (Brenner, 1992).

- A resetting of pressure-natriuresis relationship (Guyton, 1992)

- An acquired inhibition of the sodium pump (Noolfson et al, 1991).
- Nephron heterogenecity-presence of a subgroup of nephrons that is ischemic either from afferent arteriolar vasoconstriction or from an intrinsic narrowing of the lumen (Sealy et al,1998)

Vascular Hypertrophy:

A number of factors increase peripheral resistance by both functional contraction and vascular remodeling and hypertrophy. Multiple vasoactive substances act as pressure-growth promoters resulting in both vascular contraction and hypertrophy, but perpetuation of hypertension involves hypertrophy. Lever and Harrp postulated (Lever, Harrp1992) that primary hypertension has two mechanisms similar to secondary hypertension (1) a growth promoting process in children, (2) a self –perpetuating mechanism in adults.

Neurohumoral Causes of Primary Hypertension:

A large number of circulatory hormones may be involved in the development of hypertension which causes hypertension by vascular hypertrophy, capillary rarefaction and impaired microvascular dilatation (Pries, 1999).

Sympathetic Nervous Hyperactivity:

Young hypertensives tend to have increased levels of circulating catecholamines, augmented sympathetic traffic in muscles, faster heart rate and heightened reactivity to α-adrenergic agonists (White et al, 1999). These changes raise BP by causing vasoconstriction, increased cardiac output and by altering normal renal pressure-volume relationship.

Renin-Angiostension System (RAS):

Both as a direct pressor and as a growth promoter, the RAS mechanism may also be involved in the pathogenesis of hypertension. All functions of renin are mediated through the synthesis of Angiotension II. This system is the primary stimulus for secretion of aldosterone and hence mediates mineralocorticoid responses to varying sodium intake and volume overload. When sodium intake decreases or plasma volume shrinks the increase in Angiotensin II stimulates

aldosterone secretion, which causes retention of sodium and water. Increase in blood pressure inhibits release of rennin from kidney by a feed back mechanism. Thus primary hypertension would be expected to be accompanied by low renin, but only 30% have low renin while 50% have normal levels and 20% have high values. (Brunner, et al. 1973).

Hyperinsulinemia /Insulin resistance:

An association between hypertension and hyper insulinemia has been established not only in obese but also in non obese hypertension (Liese et al, 1998). The hyperinsulinemia of hypertension arises as a consequence of resistance to the effects of insulin on peripheral glucose utilization. Insulin has multiple pressor effects (Cardillo et al, 1998) including activation of sympathetic activity, trophic action on vascular smooth muscle and increased renal sodium absorption. Normally the pressor effects are counteracted by insulin mediated increased synthesis of nitric oxide. In hypertension there is impairment in the insulin mediated increase in nitric oxide leading to rise in blood pressure.

Endothelial Dysfunction

Endothelium is now known to be the source of multiple relaxing and contracting substances of which nitric oxide is an important vasodilator (Steinberg, et al, 1994). Hypertensive patients have been shown to have impaired

nitric oxide mediated vasodilatory responses (Ruschitzka, et al, 1998).

Other Associated Conditions

Hypertension is associated with other conditions like obesity, physical inactivity, sleep apnea, alcohol intake, smoking and hyperuricemia.

LEAD

The very word plumbing comes from the Latin word for lead plumbum.Symptoms of plumbism or lead poisoning were apparent as early as 1st century BC. Worldwide, six sources appear to account for most lead exposure :

1. Gasoline additives
2. Foodcan soldering
3. Lead based paints
4. Ceramic glazes
5. Drinking water systems
6. Cosmetics and folk remedies

Source

Lead has been mined and used in industry and in household products for centuries. The dangers of lead toxicity, the clinical manifestations of which are termed plumbism, have been known since ancient times. The twentieth century saw both the greatest ever exposure of the general population to lead and an extraordinary amount of new research on lead toxicity.

Populations are exposed to lead chiefly via paints, cans, plumbing fixtures, and leaded gasoline. The intensity of these exposures, while decreased by regulatory actions, remains high in some segments of the population because of the deterioration of lead paint used in the past and the entrainment of lead from paint and vehicle exhaust into soil and house dust. Many other environmental sources of exposure exist, such as leafy vegetables grown in lead-contaminated soil, improperly glazed ceramics, lead crystal, and certain herbal folk remedies. Many industries, such as battery manufacturing, demolition, painting and paint removal and ceramics, continue to pose a significant risk of lead exposure to workers and surrounding communities.

New research on lead toxicity has been stimulated by advances in toxicology and epidemiology as well as by a shift of emphasis in toxicology away from binary outcomes(life/death:50% lethal dose) to grades of function, such as neuropsychological performance, indices of behavior, blood pressure, and kidney function.

Tests for levels of lead in blood have facilitated both research on lead and surveillance of individuals at risk. Blood lead is now measured with stringent quality controls in commercial laboratories worldwide. Measurement of the blood lead levels of children 6 month to 5 years of age in mandated by some states, and the U.S Occupational Safety and Health Administration (OSHA)

requires the testing of workers who may be exposed to lead in the course of their jobs.

Metabolism

Elemental lead and inorganic lead compounds are absorbed through ingestion or inhalation. Organic lead (e.g., tetraethyl lead, the additive to gasoline) is absorbed to a significant degree through the skin as well. Pulmonary absorption is efficient, particularly if particle diameters are <1μm (as in fumes from burning lead paint). Children absorb up to 50% of the amount of lead ingested whereas adults absorb only ~10 to 20%. Gastrointestinal absorption of lead is enhanced by fasting and by dietary deficiencies in calcium, iron and zinc; such absorption is minimal, however, for lead in the form of lead sulfide, a common constituent of mining waste. Lead is absorbed into blood plasma, where it equilibrates rapidly with extra cellular fluid, crosses membranes (such as the blood-brain barrier and the placenta), and accumulates in soft and hard tissues. In the blood ~ 95 to 99% of lead is sequestered in red cells, where it is bound to hemoglobin and other components. As a consequence, lead is usually measured in whole blood rather than in serum. The largest proportion of absorbed lead is incorporated into the skeleton, which contains >90% of the body's total lead burden. Lead also appears in hair, nails, sweat, saliva, and breast milk. The half-life of lead in blood is ~ 25 days; in soft tissue, ~ 40 days; and in the nonlabile

portion of bone, >25 years. Thus, blood lead levels may decline significantly while the body's total burden of lead remains heavy.

The toxicity of lead is probably related to its affinity for cell membranes and mitochondria, as a result of which it interferes with mitochondrial oxidative phosphorylation and sodium, potassium, and calcium ATPases. Lead impairs the activity of calcium-dependent intracellular messengers and of brain protein kinase C. In addition, lead stimulates the formation of inclusion bodies that may translocate the metal into cell nuclei and alter gene expression.

Clinical toxicology

Symptomatic lead poisoning in childhood generally develops at blood lead levels>3.9 μmol/L (80μg/dl) and is characterized by abdominal pain and irritability followed by lethargy, anorexia, pallor (resulting from anemia), ataxia and slurred speech. Convulsions, coma, and death due to generalized cerebral edema and renal failure occur in the most severe cases. Sub clinical lead poisoning [blood lead level>1.4μmol/L (>30μg/dl] can cause mental retardation and selective deficits in language,cognitive function, balance, behaviour, and school performance despite the lack of discernible symptoms. Epidemiologic studies and meta-analyses of studies regarding lead's effect on the intellectual function of children indicate that cognition is probably impaired in a dose-related

fashion at blood lead levels well below 1.4 μmol/L (30 μg/dl) and that no threshold for this effect is likely to exist above the lowest measurable blood lead level of 0.05 μmol/L . The impact is greatest when the exposure is of long duration and has been most apparent when it takes place around the age of 2 years; however, the impact of fetal lead exposure remains to be clarified, particularly in view of the observation that maternal bone lead stores can be mobilized to a significant degree during pregnancy, with consequent exposure of the fetus.

In adults, symptomatic lead poisoning, which usually develops when blood lead levels exceed 3.9μg/dL) for a period of weeks,is characterized by abdominal pain, headache, irritability, joint pain, fatigue, anemia, peripheral motor neuropathy, and deficits in short-term memory and the ability to concentrate. Encephalopathy is rare. A “lead line” sometimes appears at the gingival-tooth border after prolonged high level exposure. Some individuals develop these symptoms and signs at lower blood lead levels [1.9 to 3.9 μmol/L (40 to 80μg/dL)] and or with briefer periods of exposure. Chronic sub clinical lead exposure is associated with interstitial nephritis, tubular damage (with tubular inclusion bodies), hyperuricemia (with an increased risk of gout), and a decline in glomerular filtration rate and chronic renal failure. Epidemiologic evidence also suggests that blood lead levels in the range of 0.34 to 1.7 μmol/L (7to 35 μg/dL) are associated with increases in blood pressure, decreases in

creatinine clearance, and decrements in cognitive performance that are too small to be detected as a lead effect in individual cases but nevertheless may contribute significantly to the causation of chronic disease.

An additional issue for both children and adults is whether lead that has accumulated in bone and lain dormant for years can pose a threat later in life, particularly at times of increased bone resorption such as pregnancy, lactation, and senile osteoporosis. Elevation of the bone lead level appears to be a risk factor for anemia, hypertension, cardiac conduction delays, and impairment of cognitive function. Hyperthyroidsm has been reported to cause lead toxicity in adults by mobilizing stores of bone lead acquired during childhood.

Genetic polymorphisms, such as variants of the gene that codes for aminolevulinic acid dehydratase(a critical enzyme in the production of heme) or the C282Y hemochromatosis gene,may confer differences in susceptibility to lead retention and toxicity; ~ 15% of Caucasians have a variant form of one of these genes. This issue is the focus of continued research.

Laboratory findings

In 1991, the Centers for Disease Control and Prevention designated 0.48 μmol/L(10μg/dL) as the blood lead level of concern in children. A specific set of interventions is recommended when the level exceeds this value. OSHA requires the regular measurement of blood lead in lead-exposed workers and the maintenance of blood lead <1.9 μmol/L (40 μg/dL). Concentrations of heme precursors (such as δ-aminolevulinic acid) in plasma and urine are sometimes increased at blood lead levels as low as 0.73 μmol/L (15μg/dL). Levels of protoporphyrin (free erythrocyte or zinc)rise –although not consistenly- once blood lead levels have exceeded 1.2 μmol/L (25μg/dL) for several months. Lead associated anemia is usually normocytic and normochromic and may be accompanied by basophilic stippling. Lead–induced peripheral demyelination is reflected by prolonged nerve conduction time and subsequent paralysis, usually of the extensor muscles of the hands and feet (wrist drop and foot drop). An increased density at the metaphyseal plate of growing long bones (lead lines) can develop in children and resemble those seen in rickets. Children with high-level lead exposure sometimes develop Fanconi's syndrome, pyuria, and azotemia. Adults chronically exposed to lead can develop elevated serum creatinine levels, decreased creatinine clearance rates, and chronic changes and intranuclear inclusion bodies (detected at renal biopsy). Deficits may be apparent in neuropsychometric tests of both children and adults; these abnormalities by themselves are not pathognomonic. Bone lead levels measured in vivo by K-x-ray fluorescence, a technique adapted for this purpose,

are more sensitive than blood levels as a predictor of hypertension, cognitive impairments, and reproductive toxicity in epidemiologic studies; however, measurement of bone lead levels has not been shown to be of clinical value and is not widely available.

Treatment

It is absolutely essential to prevent further exposure of affected individuals to lead. Cases of lead poisoning should be reported to local boards of health so that home evaluations can be performed. Pharmacologic treatment for lead toxicity entails the use of chelating agents, principally edetate calcium (Ca EDTA), dimercaprol, penicillamine, and succimer, which is given orally and has relatively few side effects. Chelation is recommended for the treatment of all children whose blood lead levels are >2.7 μmol/L (55 μg/dL) with the addition of dimercaprol if lead encephalopathy is found. Chelation is also recommended for children if blood lead levels are between 1.2 and 2.7 μmol/L (25 and 55 μg/dL) and the total amount of lead excreted in urine during the 8 h after a single dose of edetate calcium disodium exceeds 9.7 μmol/L (200 μg/dL). Chelation is recommended for adults if blood lead levels exceed 3.9 μmol/L (80 μg/dL) or if greater than 2.9 μmol/L (60 μg/dL) in symptomatic individuals. The ability of chelation to improve subclinical outcomes (such as performance on psychometric testing) at lower levels of blood lead in both children and adults is the subject of

current research.

In developed countries lead poisoning is not prevalent; however in developing countries lead poisoning is extremely common, to such an extent that world wide lead toxicity and poisoning remains the most common of occupational poisonings. Developed countries like the US, UK and Germany have taken aggressive steps to combat lead poisoning. In developing countries however, actions have been slower and sporadic. Within the last decade, reports of lead poisoning in humans have poured in particularly from the developing countries faced with environmental and occupational lead exposure.

In India, as in most developing countries, the main source of lead pollution is automobile exhaust; although India issued in February 1990 its first National emission standards for lead and other pollutants, the recommended permissible limits of lead (0.56g/L) are still very much higher the those of developed countries.

HYPERTENSION AND LEAD

The significant role of lead in hypertension is rapidly evolving. Studies by the environmental protection agency, as well as other international regulatory agencies, have shown that chronic low level exposure to lead is associated with societal problems such as brain dysfunction in children exposed to lead in drinking water, renal changes in adults, hypertension and chronic kidney disease.(Brautbar et al 1995,Telisman S et al 2004,Sirivarasai et al 2004). Potential effects on adult blood pressure have been described in populations encountering common environmental concentrations (Beevers et al 1976) .Other published studies (Annest J L et al, 1983) have shown that blood lead levels were related to ambient environmental exposures(Beevers et al 1980, Bost L et al 1999). Those studies showed a direct relationship between blood pressure elevation and low level toxicological exposure to lead without the classical

presentation of lead toxicity (Annest J L et al, 1983). A study in the United States looked at the relationship between blood lead level and high blood pressure and found a direct relationship between blood lead levels and systolic and diastolic blood pressure for men and women, and that blood levels of lead were significantly higher in younger men and women with high blood pressures (Harlan W R 1985). Beevers et al (1980), in an interesting study found that blood lead levels correlate with hypertension in persons exposed to hard water and not in those exposed to soft water. They concluded that low grade exposure from water leads to increased blood lead levels and hypertension.

It is of importance to note that in all of these studies the blood pressure was correlated with slightly elevated lead levels which have been considered to be "safe" and are the result of low level cumulative exposure to lead. These studies indicate very clearly that blood lead levels were found to contribute independently to the elevation of systolic and diastolic hypertension. In some studies bone lead levels were used to measure chronic low level exposure to lead and were found to be elevated in hypertensives. (Cheng et al , 2001) (Stassen et al 1992).

Multiple sources of exposure exist including occupational, ambient environmental and consumption of water from lead piping which all contribute to elevation of blood lead levels .Most thinking about lead exposure and

hypertension has usually been directed towards excessive occupational exposure and effects of lead and kidney function, kidney compromise and in turn, effects on high blood pressure. In a study Lee (1996) found that each 10 fold increase in blood lead level was associated with a serum creatinine increase of 0.08mg/dL.

Tsaih et al 2004, says that longitudinal decline of renal function among middle aged and elderly individuals appears to depend on both long-term lead stores and circulating lead. Other studies also concentrate on lead induced nephrotoxicity and hypertension (Pirkle et al, 1985) (Hu H ,2000) (Batuman V, 1993).

There is more and more evidence that chronic low level toxicological exposure to lead has both direct and indirect effects on the blood vessel and its smooth muscle's contractility and thereby affecting the blood pressure.

Some authors find no statistically significant difference in blood lead levels with respect to target organ damage like left ventricular hypertrophy (Tepper et al 2001)

Mechanism of lead induced hypertension

Chronic lead exposure basically targets catecholamine and nitric oxide

systems in inducing selective functional impairment. Cormignani etal (2000) have conducted a study in which rats were exposed for ten months to 60 ppm of lead (Pb acetate) in drinking water and the cardiovascular effects of chronic lead were assessed. At the end of treatment, mean lead levels were increased in lead exposed rats. The conclusions derived from their study were:

1. Lead increases plasma levels of noradrenaline and adrenaline
2. Lead increases monoamine oxidase activity in aorta and liver
3. Plasma level of nitric oxide decreases
4. Increases peripheral resistance, cardiac inotropism
5. Increases cAMP dependent availability of Ca ions for contractile mechanism in vascular and cardiac myocells
6. Also increases vascular alpha-2 and myocardial B1 adreno receptor reactivity
7. Also inhibits Kallikrein- Kinin and RAA systems

It was thus concluded that lead appeared to increase sympathetic activity both by central and peripheral mechanisms .Sharifi et al (2004) have conducted a similar study in rats and proposed several mechanisms to explain lead induced hypertension. They have investigated the etiological role of RAS and ACE activity in this context. This study also revealed that BP gradually increases in correlation with lead exposure. There was also a significant increase of local and

serum ACE activity in the early phase of lead exposure thus emphasizing the etiological role of ACE activity in lead induced hypertension.

Various similar studies have been conducted in humans to find out the effects of chronic low level lead exposure in the causation of hypertension. A study was conducted by Schwartz et al (2000) in former organolead manufacturing workers to determine the influence of blood lead, DMSA, (meso 2,3-dimercapto succinic acid) chelatable lead and tibial lead on systolic and diastolic blood pressure. They found that blood lead was a predictor of both systolic and diastolic blood pressure and hypertensive status in men less than 58 yrs.

Thus the pathogenesis of lead induced hypertension in multifactorial including such diverse mechanisms as

- Inactivation of endogenous nitric oxide. (Vaziri et al, 2004; Apostoli et al, 2004)
- Down regulation of soluble guanylate cyclase by reactive oxygen species leading to functional deficiency of nitric oxide.
- Heightened sympathetic activity and plasma noradrealine.
- Decreased vascular and increased renal beta adreno receptor density (Chang H R, 2005)
- Increased plasma ACE activity, plasma renin activity, angiotensin II and aldosterone level

- Increased kininase I and kininase II activites .

- Lead induced inhibition of vascular smooth muscle Na K ATPase causing increased cellular Na^{+} ,Ca^{2+}
- Possible increase in endothelin and TXA2 generation
- Increase in vasoconstrictive prostaglandins and decrease in vasodilatory prostaglandins.

From the review the following conclusions were arrived at :

The available scientifically reviewed data described above shows that exposure to low levels of lead on a repetitive basis in some population and in some patients can be associated with high blood pressure. These issues of high blood pressure and neurobehavioral charges in relation to lead exposure are commonly missed, not looked for in patients who present with low level toxicological exposure to lead. There is little controversy regarding the issue that lead levels is clinically significant and relevant although its role as an independent risk factor in the causation of hypertension may be controversial.

From a clinical standpoint, a practising doctor should not forget the concept of low level toxicological exposure to lead. He should not always concentrate on the classic presentation of lead toxicity. A prudent physician has to take into account and address the issue of environmental lead exposure while

treating patients.

The current focus of attention is on the subclinical effects of exposure. There is pressure to reduce lead exposure in general population and in working environment (Gidlow DA2004).

MATERIALS AND METHODS

Setting : Government Rajaji Hospital and
Madurai Medical College, Madurai

Collaborating : School of Energy Sciences

Department : Department of Environment
Madurai Kamaraj University, Madurai

Study Design : Case control study

Period of Study : August 2004 to August 2005

Sample Size : 60 Subjects

Ethical committee : The present project was approved by the approval ethical committee

Inclusion criteria:

Cases:

1. Newly diagnosed drug naïve hypertensive patients attending Out patient(O.P) clinic .
2. Patients between ages 30-50yrs.
3. Both sexes.

Controls:

Other patients of the same age group attending the O.P clinic.

Exclusion criteria:

1. Individuals less than 30 and more than 50years
2. Patients with renal failure and diabetes mellitus
3. Pregnant women.
4. Patients with secondary hypertension
5. Patients who were already on antihypertensive therapy
6. Postmenopausal women
7. Patients exposed to certain occupations, industries where lead concentration is high (e-g) painters, plumbers etc.

Controls

Subject whose ages were between 30 yrs and 50 yrs and had normal blood pressure.

Consent

The study group thus identified by the above criteria (inclusion and exclusion criteria) were first briefed about the nature of the study. Willing participants were taken up after getting a written informed consent from them.

Materials

Thus a total of 30 cases who satisfied the inclusion and exclusion criteria above were taken up for the study. 30 age and sex matched subjects were kept as controls.

Conflict of interest

There was no conflict of interest

Financial support

Nil

Limitations

1. Only drug naïve newly diagnosed hypertensive patients were included in the study. Patients who were already on antihypertensive drugs were not studied.

2. Due to technical, financial and ethical constraints, blood lead levels of only 30 cases and 30 controls could be measured.

3. Only blood lead levels were measured. Bone lead levels, which is the most valuable measure of internal dose (as it represents cumulative exposure) and which is a more accurate and sensitive marker to assess chronic low level environmental pollution was not done. Currently the most effective

method to measure bone lead involves in-vivo K-X-ray fluorescence which is expensive and time consuming. It is not practical for studies and hence was not done.

4. Due to literary constraints, original copy of all the articles could not be obtained. Only abstracts of those articles were obtained.

5. Cigarette smoking and urbanization as confounding factors were not eliminated.

6. It is only a cross sectional study. Long term follow up was not done.

7. Vancouver's method of Bibliography was not followed. Instead Harvard method was followed.

Methods:

Selected socio-demographic, clinical and laboratory data were elicited from the patients and controls and recorded in a proforma (enclosed in Annexure –annexure I)

I. Socio –demographic data

Age

Sex

II. Clinical data

Systolic and diastolic blood pressure

Clinical examination

III. Laboratory data

Blood urea : Estimation done manually using Diacetyl Monoxime (DAM) technique.

Serum Creatinine : Estimation done using COBAS autoanalyser

Blood lead levels : Measured using atomic absorption Spectro Photometry

IV. Statistical Analysis

Data was entered in Microsoft excel spread sheet and analyzed statistically using standard statistical software (Epidemiological information package 2002). Student 't' values was applied for significance. Significance was considered if the 'p' value was below 0.01.

DEFINITIONS USED IN THE PRESENT STUDY

Essential Hypertension

Hypertension was defined in accordance to the JNC-VII report as systolic

blood pressure 140 mmHg and above and or diastolic blood pressure 90mm Hg above.

In newly detected cases it was the mean of 3 relaxed, seated right arm readings. The diagnosis that the hypertension is essential and not secondary was made on the overall clinical impression only. Laboratory investigations to rule out secondary causes was not done in each case.

Diabetes mellitus

- Already a known case of diabetes mellitus on treatment
- Fasting plasma glucose ≥126 mg/dl
- Two hour plasma glucose ≥200mg/dl
- Symptoms of diabetes plus random blood glucose >200 mg/dl

Left ventricular hypertrophy

Based on electrocardiographic findings satisfying either Sokolow-Lyon criteria or Cornell Voltiye criteria (Sokolow, Lyon,1949) (Casale, et.al,1987).

Hypertensive retinopathy

Based on Keith- Wagener-Barker classification of fundoscopic changes.

RESULTS

The total number of subjects included in this study was 60.Among these 60 subjects, 30 were cases (hypertensive) and 30 were control (normotensive)

Table – 1

Age distribution of cases and controls

	Cases		Controls	
Age group	No	%	No	%
30-40	5	16.6	7	23.3
40-50	25	83.4	23	76.7
Total	30	100	30	100
Mean age	45.9		43	
SD	5.73		4.24	

p value = 0.0325

This table compares the mean age of cases and controls. There is no statistically significant difference in the ages of cases of controls. Hence the study is matched for age.

Table – 2

Sex distribution of cases and controls

	Cases		Controls	
Sex	No	%	No	%
Male	19	63.3	18	60
Female	11	36.7	12	40

Total	30	100	30	100

This table compares the sex distribution in cases and controls. There is no significant difference in the distribution with respect to sex.

Table – 3

Blood Pressure Distribution among cases

BP	**Cases**	
	Mean mm/Hg	**SD**
Systolic	166.66	25.37
Diastolic	105.33	16.55

The mean and standard deviation for systolic blood pressure among cases were 166.66 and 25.37 respectively. Similarly for diastolic blood pressure the mean and S.D among cases were 105.33 and 16.55 respectively.

Table – 4

Distribution of cases and controls in relation to smoking

	Cases		**Controls**	
	No	**%**	**No**	**%**
Yes	13	43.3	14	46.6
No	17	56.67	16	53.4
Total	30	100	30	100

In the study population the distribution of smoking is not significantly different among cases of controls.

Table – 5

Distribution of cases and controls with respect to

Target Organ Damage (TOD)

TOD		Cases	
		No	**Percentage**
LVH	**Yes**	12	40
	No	18	60
IHD	**Yes**	2	6.3

	No	28	93.7
HPR	**Yes**	6	20
	No	24	80

The details of prevalence of target organ damage TOD among cases [left ventricular hypertrophy (LVH), Ischemic heart disease (IHD) and hypertensive retinopathy HTR] are given.

Analysis of cases with respect to target organ damage revealed the presence of various target organ damage in the form of

Left ventricular hypertrophy LVH (n=12 ; 40%)

Ischemic heart disease IHD (n=2 ; 6.3%)

And hypertensive retinopathy (n=6; 20%)

Table – 6

Distribution of cases and controls with respect to biochemical parameters

Blood parameters	**Cases**		**Controls**		**P**
	Mean	**SD**	**Mean**	**SD**	
Bl.sugar	103.8	21.9	86.2	± 6.20	0.000101
Urea	27.36	4.48	24.93	± 2.40	0.0126
Creatinine	0.80	0.09	0.78	± 0.08	0.3748

There is a statistically significant difference in cases and control with respect to blood sugar and urea. This may be due to high comorbidity of impaired glucose tolerance in hypertensives. But with respect to creatinine which is more sensitive marker for renal function and also could be a confounding factor in hypertension, there is no statistically significant difference between cases and controls. Hence, there is no much difference with respect to renal function between cases to controls.

Table – 7

Distribution of cases and controls in relation to blood lead levels

	Cases		**Controls**		**p value**
	Mean	**SD**	**Mean**	**SD**	
Bl.Pb levels µg/dl	25.34	± 7.59	7.36	± 3.62	0.0000001

Using students 't' test P value <0.01 t=11.5 df 58

The mean blood level is 25.34 µg/dl (SD 7.59) in cases and 7.36 µg/dl (SD 3.62) in controls. This table clearly shows that blood lead level is significantly higher in hypertensive patients.

Table – 8

Distribution of blood lead levels ≥10 µg /dl in cases and controls

	Cases				Controls			
	No	**%**	**Mean**	**SD**	**No**	**%**	**Mean**	**SD**
Bl.Pb levels≥10 µg/dl	30	100	25.34	±7.59	11	36.7	11.4	±1.22

P=0.0000001

As a blood lead level of 10µg/dL is defined as the level of concern by many authorities, (Hu et al, 2001) the distribution of blood lead level ≥10µg/dL was sought.

All cases had blood lead level ≥ 10µg/dL while 11 (36.7%) controls had blood lead level ≥10µg/dL. All these controls were found to be smokers. Hence this explains increased blood lead levels in them. Using students 't' test p was found to be < 0.01.

Hence the prevalence of high blood lead level above the level of concern is statistically high in cases than in controls.

Table – 9

Mean Pb levels in relation to sex

	Cases			**Controls**			
	Pb levels (µg/dL)			**Pb levels (µg/dL)**			
Sex	**No**	**Mean**	**SD**	**No**	**Mean**	**SD**	
M	**19**	27.73	± 7.69	18	9.32	± 3.21	t=9.3325 df 35 P=0.0000001
F	**11**	21.21	± 5.58	12	4.41	± 1.73	t=9.1303 df 21 P=0.00000001

			t=2.5775 df 28 P=0.01			t=5.234 df 28 P=0.0000144	

From the table it can be seen that in both cases and controls there is statistically significant difference in blood lead levels between males and females.

This could be due to the effect of smoking on blood lead levels.

But compared with controls in either sex the cases have statistically significant high values in blood lead levels.

Table – 10

Smoking and Blood lead levels

Blood lead level in µg/dL

	Cases			**Controls**			
Smoking	**No**	**Mean**	**SD**	**No**	**Mean**	**SD**	
Yes	13	30.55	7.68	14	10.7	1.75	t=8.7840 df 35 P=0.000001
No	17	21.36	4.62	16	4.36	1.49	t=13.964 df 31 P=0.0000001
			t=3.51 df 23			t=10.2367 df 28	

			P=0.001			P0.0000001	

This table clearly shows that there is statistically significant difference in blood lead levels among smokers and non smokers.

In cases ($p = 0.01$) as well as in controls ($p < 0.001$) smoking is associated with high blood lead levels.

Table – 11

Blood lead levels with respect to target organ damage TOD

The mean blood lead levels and standard deviation for cases with and without target organ damage is given below.

TOD		**No**	**Mean (µg/dL)**	**SD**	**P**
LVH	Yes	12	29.69	± 7.80	0.014 [df 28 t =2.61]
	No	18	22.45	± 6.06	
IHD	Yes	2	27.35	± 3.74	0.5962 [df 28

					t =0.53]
	No	28	25.20	± 7.81	
Retinopathy	Yes	6	31.61	± 9.53	0.0898 [df 28 t =1.757]
	No	24	23.77	± 6.33	

With regards to target organ damage, though there is some increase in blood lead levels in those with target organ damage compared to those without, the difference is not statistically significant.

(P values were 0.014, 0.59, 0.08 respectively with reference to LVH, IHD & HTR).

DISCUSSION

Hypertension, the most common form of cardiovascular diseases, is one of the most important risk factors for significant morbidity and mortality in human race. Though the cause of essential hypertension is elusive, lead is associated with hypertension.

A number of studies have found that increased blood lead levels strongly correlate with increased systolic as well as diastolic blood pressure (Brautbar et al, 1995; Telisman et al, 2004; Sirivarasai et al, 2004).

In addition chronic low level exposure to lead causes increased blood pressure without overt manifestations of lead toxicity (Annest J.L. et al ,1983; Harlan WR et al, 1985)

Tepper et al,(2001) also found increased blood lead levels in hypertensive patients compared to normotensives.

Sirivarasai (2004) in a study of 212 men found that an increase in blood pressure was significantly predictive of increasing blood lead ($p<0.001$)

Similar to those studies, in our study, the mean lead value was 25.34 µg/dl ±7.59 among cases and 7.36 µg/dl ± 3.62 among controls. Thus there is statistically significant increase in blood lead levels in hypertensives compared to normotensives in our study.

Some studies found a correlation between blood lead levels and hypertension only in selected populations.

Vupputuri et al (2003) found high blood level only in hypertensive black men.

Beevers et al in 1980, found a positive correlation between blood lead level and hypertension in an environmental survey, though this effect was seen only in persons exposed to water with high lead level. Hence he concluded that cumulative exposure of lead from drinking water is a source of hypertension.

In our study due to technical constraints, the effect of lead present in drinking water on blood lead levels could not be studied.

In some studies blood lead levels do not correlate with hypertension. Cheng et al (2001) and Telisman et al (2004) found no correlation between blood lead levels and hypertension .But they have found strong correlation between bone lead level (which measures chronic low grade exposure) and hypertension .But those studies were done in developed countries. Exposure to lead and hence blood lead level vary greatly between countries depending upon the environment.

The mean blood lead value was 25.34 µg/dl for cases and 7.36 µg/dl for controls in our study. When we compare this with other studies this is higher. In Vupputuri et al (2003) study the mean blood lead value was 5.4 ± 0.2 for men and 3.4 ± 0.1 for women.. Schwartz et al (2000) also found increased blood pressure in patients with blood lead level as low as 5 µg/dl.

High values in our study could be due to high exposure to lead in developing countries in the form of smoke, industrial waste and through water (Beevers et al, 1980). But in developed countries the blood lead levels are coming down due to increasing awareness (Vupputuri et al, 2003).

The percentage of persons above blood lead level 10 µg/dl in cases is100% where as in controls it is 36.7%. All those controls were smokers. Though absolutely no blood lead level is safe, many authorities have defined a level of 10 µg/dl as a value of concern (Hu 2001).Hence it can be said that hypertensive patients have blood lead level above the level of concern.

In our study, there is also a significant sex difference in blood lead levels . From table 9 it is seen that in both cases and controls, males have high blood lead values than controls. This is similar to the studies of Vupputuri et al(2003)(Men 5.4±0.2 women 3.4±0.1 $p<0.001$). The difference could be due to many factors. Men are more exposed to smoke, industrial pollution, automobile exhaust etc., than women. The values are still higher in developing countries due to men exposed to higher level of environmental lead.

Cigarette contains lead and cigarette smoking may contribute significantly to increased blood lead levels. Table 10 shows that in both cases and controls there is statistically significant difference in blood lead levels among smokers and non smokers. Smoking is a risk factor for adverse coronary events. The elevation of blood lead level and indirectly of blood pressure may be one of the mechanisms of action of cigarette smoking causing atherosclerosis.

With reference to target organ damage, in our study, there was a slight increase in blood level among those with target organ damage compared with those who do not. The difference , however, is not statistically significant. Tepper et al (2001) has similar findings in his study. There was no convincing evidence of association between lead and other blood pressure related outcomes in his study, though there was an effect of blood lead on blood pressure.

Blood pressure is clearly increased by high blood lead levels in our study. Blood lead level is increased by chronic low grade exposure and the prohypertensive effect of lead occurs at blood lead levels which are very much below those that are associated with clinically significant symptoms like neurological behavioral manifestations.Hence the need to identify patients exposed to sub threshold values becomes important. This is much more important in developing countries with high environmental exposure and less rigid pollution control measures. Identifying & intervening hypertensives with high lead levels at an early stage may halt the progress of a debilitating illness.

Measurement of lead exposure can be difficult as more accurate methods like measuring bone-lead levels are not available freely. More studies in this area and more prospective studies with respect to outcome measures are the need of the hour.

CONCLUSIONS

1. Blood lead level was significantly elevated in persons with hypertension (Mean 25.34±7.59 μg/dL) than normotensive controls (Mean 7.36±3.62 μg/dL).

2. Blood lead level was ≥ 10 μg/dL in all the cases(100%).In controls it was 36.7%. Blood lead level of 10μg/dL is defined as the value of concern by many.

3. There is a statistically significant difference between males & females with respect to blood lead values in both cases and controls.

   Cases : Males → 27.73 ± 7.69 μg/dL ; Females → 21.21 ± 5.58 μg/dL

   Controls : Males → 9.32 ± 3.21 μg/dL ; Females → 4.41 ± 1.73 μg/dL

4. There is a statistically significant difference between smokers and non-smokers with respect to blood lead levels in both cases as well as controls.

   Cases: Smokers → 30.55 ± 7.68 μg/dL ; Non Smokers → 21.36 ± 4.62 μg/dL

   Controls: Smokers → 10.7 ± 1.75 μg/dL ; Non Smokers → 4.36 ± 1.49 μg/dL

5. Blood lead levels were not significantly elevated in patients with target organ damage compared to those without.

SUMMARY

Blood lead level strongly correlates with hypertension. The present study was aimed to study the blood lead level in patients with primary hypertension and to find out its association with sex, smoking status and target organ damage. With rigid criteria 30 patients were selected and evaluated on social, clinical and laboratory aspects after institutional ethical clearance with an informed consent. The data were entered in computer and analyzed statistically.

The controls were matched for age and sex compared to cases. There were 19 males and 11 females in the case group and 18 and 12 respectively in control group. The mean systolic BP was 166.66 mmHg and 105.33mmHg diastolic.

The mean lead levels were significantly higher in hypertensives (Mean 25.34 ±7.59 μg/dL) compared to controls (7.36±3.62 μg/dL). The percentage of persons with blood lead levels > 10 μg/dL is also greater in cases than in controls (100% Vs 36.7%). There is also a statistically significant difference in blood lead values among smokers and non smokers in both cases and controls. (Cases :smokers 30.55 ± 7.68 μg/dL non smokers 21.36 ± 4.62 μg/dL; Controls : smokers 10.7 ± 1.75 μg/dL, non smokers 4.36±1.49 μg/dL). There is also a statistically significant difference between males and females in both cases and controls [Cases: males 27.73±7.69 μg/dL; females 21.21 ± 5.58 μg/dL ;Controls :males 9.32 ± 3.21 μg/dL ;females 4.41 ± 1.73 μg/dL].

The percentage of those with target organ damage were 40%, 6.3% and 20% respectively for LVH, IHD and retinopathy. There is no correlation between increased blood level between those with and without target organ damage.

Animal & human studies have found correlation between blood lead levels and hypertension. In view of the increased industrialization and poor environmental surveillance, it is prudent to explore blood lead levels in hypertensives especially those with chronic low grade exposure.

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PROFORMA

Name : Age: Sex: Occupation:

Presenting Complaints : Duration:

Chest Pain

Breathlessness

Palpitation

Giddiness

Headache

Smoking

Physical examination :

Anemia Cyanosis Pedal edema JVP

PR BP Fundus

Systemic Examination

CVS : Apical impulse position

Character

Thrill / Murmur

S_1S_2

A_2 intensity

RS

P/A

CNS

INVESTIGATIONS

Blood Sugar ECG

Urea

Serum Creatinine

X-ray Chest PA view Blood Lead Levels