

# **TRACE ELEMENT STUDIES ON KARACHI POPULATION PART IV: BLOOD COPPER, ZINC, MAGNESIUM AND LEAD LEVELS IN PSYCHIATRIC PATIENTS WITH DEPRESSION, MENTAL RETARDATION AND SEIZURE DISORDERS**

Pages with reference to book, From 269 To 274

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## **Abstract**

Blood copper, zinc, magnesium and lead levels were determined by atomic absorption spectroscopy for 15 males and 16 females suffering from depression, 6 males and 1 female with mental retardation and 3 males and 4 females with seizure disorders. They were all under no medication and belonged to low income groups. No difference in copper levels was found between the sexes in any of the groups. The levels in all the groups were significantly higher than in the normals. In depressives, males had significantly higher zinc levels than females and only female depressives had significantly different (lower) levels from normals. In both depressives and normals, males had higher magnesium levels than females but no group of patients had significantly different levels from normals. Lead levels were significantly higher in female depressives and for those with seizure disorders than for controls. At least one metal abnormality was found in 21(67.7%) depressive, 5 (71.4%) of those with mental retardation and 6 (85.7%) with seizure disorders (JPMA 39 : 269, 1989).

## **INTRODUCTION**

Lead is associated with a whole host of neurological, physiological and behavioural problems, and some of the important points concerning these have been briefly discussed previously<sup>1</sup>. In cases of depression one would expect blood copper levels to be the opposite to those in hyperexcitability<sup>2</sup>, namely, that these levels should be lower than normal. Both high<sup>3</sup> and low levels<sup>2,4</sup> have been reported for schizophrenics. For mental retardation, we have found no literature references but in those with seizure disorders excitatory neurotransmitter functions dominate and copper levels should be raised<sup>2</sup>. On the basis of high zinc levels being associated with hyperexcitability<sup>2</sup>, depression should predictably be associated with zinc deficiency. In fact, this has been found not only for depression<sup>4</sup> but also for thought disorders and schizophrenia<sup>3,4</sup> and also in neuronal undevelopment due to maternal or infant malnutrition<sup>2</sup>. Seizure disorder cases would be expected to have high zinc levels<sup>2</sup>. Raised blood levels of magnesium are associated with CNS depression<sup>4</sup> and schizophrenias have variously been reported as being associated with either high<sup>5,6</sup>, low<sup>7</sup> or normal levels<sup>8,9</sup>. We have found nothing reported for those with mental retardation, but those with seizure disorders should have low levels<sup>4</sup>. We have found no satisfactory explanation in the literature as to how these metal abnormalities are connected to the disease states.

## **MATERIALS, EQUIPMENT AND METHOD**

Estimation of copper, zinc and magnesium on whole blood was by atomic absorption spectroscopy, and details of the method and selection of control subjects has been described in Part I of this series<sup>10</sup>. Lead was estimated similarly to copper and zinc.

### Patients

Patients belonged to the low income groups attending the outpatients neuropsychiatric clinic at the Jinnah Postgraduate Medical Centre, Karachi for the first time. They were under no medication at the time of blood sampling. They were of three categories, those suffering from depression (15 males and 16 females), those with mental retardation (6 males and one female), and those suffering from seizure disorders (3 males and 4 females). As the second and third groups were small, results for these were not considered by sex.

### Statistical Analysis

Distribution of metal levels in every case was non-Gaussian. Therefore the Student's 't' test for significance of difference was invalid and the Wilcoxon Rank Sum Test was used. Regression analysis was performed as previously.<sup>10</sup>

## RESULTS

Relevant information concerning blood levels of copper, zinc and magnesium for the patients is given in Tables I-VI

**TABLE I. Blood Copper Ranges for Normals and Patients.**

Group	Sex	Median ug/dl	Mean ug/dl	Range ug/dl	S.D.	P
Normals <sup>11</sup>	M + F	94.5	93.5	71-116	11.25	0.05 <sup>+</sup>
Depressives	M	116.5	117.1	85-178	24.3	0.05 <sup>+</sup> 0.01 <sup>*</sup>
	F	102.1	112.1	86-161	23.2	
	M + F	110.5	114.0	85-178	23.4	
Mentally Retarded	M + F	115.9	116.0	89-148.5	20.4	0.01 <sup>*</sup>
Seizure Disorders	M + F	101.8	118.5	87-171	32.4	0.05 <sup>*</sup> 0.01 <sup>*</sup>

\*Significance of difference with normals.

+Significance of difference between males and females.

**TABLE II. Normal and Abnormal Levels for Copper for the Patients.**

Group	Sex	N	Low Levels	Normal Levels	Raised Levels
Depressives	M	14	0	7(50.0%)	7(50.0%)
	F	16	0	10(62.5%)	6(37.5%)
	M + F	30	0	17(56.6%)	13(43.3%)
Mentally Retarded	M + F	6	0	3(50.0%)	3(50.0%)
Seizure Disorders	M + F	7	0	4(57.0%)	3(42.9%)

**TABLE III. Blood Zinc Ranges for Normals and Patients.**

Group	Sex	Median (ug/dl)	Mean (ug/dl)	Range (ug/dl)	S.D.	P
Normals <sup>10</sup>	M	726	726	602.5-850	61.9	<0.01 <sup>+</sup>
	F	695.5	685.9	519-853	83.5	
	M + F	705.0	711.0	563-859.5	74.1	
Depressives	M	727.0	730.4	573-1052	114.5	> 0.05*
	F	651.8	649.7	426-802	96.5	<0.05 <sup>+</sup>
	M + F	691.0	688.7	426-1052	111.6	>0.01 <sup>+</sup> *
Mental Retardation	M + F	762.0	752.6	612-870	93.3	<0.05 <sup>+</sup>
Seizure Disorders	M + F	679.0	685.9	564-840	99.7	>0.01* > 0.05*

\*Significance of difference with normals.

+Significance of difference between males and females.

**TABLE IV. Normal and Abnormal Levels for Zinc for the Patients.**

Group	Sex	N	Low Levels	Normal Levels	Raised Levels
Depressives	M	15	2(13.3%)	12(80.0%)	1(6.7%)
	F	16	2(12.5%)	14(87.5%)	0
	M + F	31	4(12.9%)	26(83.9%)	1(3.2%)
Mental Retardation	M + F	7	0	6(85.7%)	1(14.3%)
Seizure Disorders	M + F	7	1(14.3%)	6(85.7%)	0

**TABLE V. Blood Magnesium Ranges for Normals and Patients.**

Group	Sex	Median (mg/dl)	Mean (mg/dl)	Range (mg/dl)	S.D.	P
Normals <sup>10</sup>	M	3.80	3.78	2.97-4.80	0.46	< 0.05 <sup>+</sup>
	F	3.51	3.50	2.65-4.66	0.50	
	M + F	3.60	3.61	2.75-4.80	0.51	
Depressives	M	4.14	4.33	2.94-6.53	1.11	> 0.05*
	F	3.56	3.75	2.66-6.265	0.50	< 0.05 <sup>+</sup>
	M + F	3.74	4.02	2.66-6.53	0.96	> 0.01 <sup>+</sup> *
Mental Retardation	M + F	3.78	4.39	3.29-6.79	1.32	> 0.05*
Seizure Disorders	M + F	3.99	4.20	3.185-5.56	1.00	> 0.05*

\*Significance of difference with normals.

+Significance of difference between males and females.

**TABLE VI. Normal and Abnormal Levels for Magnesium for the Patients.**

Group	Sex	N	Low Levels	Normal Levels	Raised Levels
Depressives	M	14	1(7.1%)	9(64.3%)	4(28.6%)
	F	16	0	16(100%)	0
	M+F	30	1(3.3%)	25(93.3%)	4(13.3%)
Mental Retardation	M+F	7	0	5(71.4%)	2(28.6%)
Seizure Disorders	M+F	7	0	5(71.4%)	2(28.6%)

together with that for the normal subjects reported previously. 10 Ten (5 males, 5 females) of the 31 patients (32.3%) with depression had no blood metal abnormality (Table VII)

**TABLE VII. Number and Percentage of Metal Abnormalities among the Patients.**

Group	Sex	n	Number of Metal Abnormalities							
			0*	0+Pb*	1*	1+Pb*	2*	2+Pb*	3*	3+Pb*
Depressives	M	15	5(33.3%)	1(6.7%)	3(20.0%)	1(6.7%)	4(26.7%)	0(0%)	0	0
	F	16	5(31.25%)	3(18.75%)	4(25.0%)	4(25.0%)	0	0	0	0
	M+F	31	10(32.3%)	4(12.9%)	7(22.6%)	5(16.1%)	4(12.9%)	0	1(3.2%)	0
Mental Retardation	M+F	7	2(28.6%)	1(14.3%)	1(14.3%)	1(14.3%)	1(14.3%)	1(14.3%)	0	0
Seizure Disorders	M+F	7	1(14.3%)	2(28.6%)	1(14.3%)	2(28.6%)	0	0	0	1(14.3%)

\*Copper, zinc and/or magnesium but lead below 40 ug/dl.

+ Copper, zinc and/or magnesium and lead over 40 ug/dl.

and 21 (10 males, 11 females) or 67.7% had at least one. Four patients (1 male, 3 females) or 12.9% had lead levels of 40 ug/dl or over with no other metal abnormality and five (1 male, 4 females) or 16.1% had lead plus one other metal abnormality. One male had three metal abnormalities: copper, zinc and magnesium. Lead levels of 40 ug/dl or over were taken as "abnormal", although levels of over 25 ug/dl should really be regarded as "elevated" 11. For other metals, "abnormal" meant a high or low blood level Of the seven patients with mental retardation, two (28.6%) had no metal abnormality, five (71.4%) had at least one abnormality including one (14.3%) with an abnormal lead level only and two others with lead plus at least one other metal abnormality. Of the seven with seizure disorders, the corresponding figures were one (14.3%), six (85.7%), two (28.6%) and three (42.9%) respectively. The levels of all four metals were abnormal in one male. As in the normals, there was no significant difference in blood copper levels between the sexes in the depressive group. Levels were significantly higher, as were those with mental retardation ( $p < 0.01$ ) and with seizure disorders ( $0.05 > p > 0.01$ ) than the normals (Tables I and II). Male depressives had significantly higher zinc levels than female patients ( $0.05 > p > 0.01$ ) as in normals (Tables III and IV). There was no significant difference in the levels between male patients and normal males but levels for female, and male and female patients combined were significantly lower than for the corresponding normals ( $0.05 > p > 0.01$ ). For mental retardation and seizure disorders, levels were not significantly different to those of normals. Male depressives had significantly higher blood magnesium levels than female patients ( $0.05 > p > 0.01$ ) as in normals (Table V and VI) but there was no significant difference bysex between patients and normals. Levels were not significantly different to normals in mental retardation and seizure disorders. Females in the depressives group had higher lead levels than males ( $p = 0.05$ ). There was no significant difference

between the levels for male patients and controls, but female patients had higher levels than the corresponding controls ( $0.05 > p > 0.01$ ) as did males and females combined ( $p = 0.05$ ). Eight (2 males, 6 females) of the 31 patients (25.8%) had abnormal levels (at or above 40 ug/dl). The 7 patients with mental retardation did not have significantly higher levels than controls, although 3 males (42.9% of the total) had abnormal levels. Levels were significantly higher for the 7 with seizure disorders ( $p = 0.01$ ) and 2 males and 3 females (71.4% of the total) had abnormal levels. Regression analysis was carried out as previously<sup>1</sup> results being in

**TABLE VIII. Intermetallic Regression Equations and Correlation Coefficients for Patients and Normals.**

Metals	x	y	Sex	Regression Equation	Correlation Coefficient (Patients)	Correlation Coefficient (Normals)
<b>Depressives</b>						
Zn V. Cu	Cu	Zn	M	$y = 1.694x + 531.5$	0.346	-0.247
			F	$y = 1.869x + 440.3$	0.449	0.095
			M+F	$y = 1.954x + 463.6$	0.405	-0.108
Mg V. Cu	Cu	Mg	M	$y = 0.0273x + 1.422$	0.652	0.320
			F	$y = 0.00336x + 3.200$	0.157	-0.209
			M+F	$y = 0.0174x + 2.079$	0.435	-0.042
Mg V. Zn	Zn	Mg	M	$y = 4.002x \cdot 10^{-3}x + 1.590$	0.427	-0.0479
			F	$y = -0.3424x \cdot 10^{-3}x + 3.799$	-0.0667	0.367
			M+F	$y = 3.390x \cdot 10^{-3}x + 1.695$	0.396	0.249
<b>Mental Retardation</b>						
Zn V. Cu	Cu	Zn	M+F	$y = -2.099x + 987.2$	-0.433	-0.108
Mg V. Cu	Cu	Mg	M+F	$y = -0.00717x + 5.263$	-0.142	-0.042
Mg V. Zn	Zn	Mg	M+F	$y = -4.567x \cdot 10^{-3}x + 7.825$	-0.324	0.249
<b>Seizure Disorders</b>						
Zn V. Cu	Cu	Zn	M+F	$y = 2.107x + 436.1$	0.685	-0.108
Mg V. Cu	Cu	Mg	M+F	$y = 0.00239x + 3.919$	0.0771	-0.042
Mg V. Zn	Zn	Mg	M+F	$y = -76.93x \cdot 10^{-3}x + 4.730$	-0.0764	0.249

Table VIII and metal abnormalities on an individual basis and grouped according to diagnosis or manifestations of disease are in Table IX.

TABLE IX. Metal Abnormalities in Diagnosed Cases and in some Individual manifestations.

Diagnosis or Manifestation	Sex	N	Number of Metal Abnormalities				
			None	One	Two	Three	Four
Depressive Phase	F	3		(1) Cu ↑ (2) Zn ↓	(3) Zn ↓ Pb ↑		
Schizo. + Depressive	M	2	(1)	(2) Zn ↓			
Psychomotor Retardation	M	1			Cu ↑ Pb ↑		
	F	2	(1,2)				
Lethargy, headaches, etc.	M	6	(1,2)	(3) Pb ↑	(4) Cu ↑ Zn ↓ (5) Cu ↑ Mg ↑	(6) Cu ↑ Zn ↑ Mg ↑	
	F	2		(1) Cu ↑	(2) Cu ↑ Pb ↑		
Agitated Depressives	M	3	(1,2)		(3) Cu ↑ Mg ↑		
	F	2	(1)	(2) Pb ↑			
Weeping Spells, withdrawn etc.	M	3		(1) Mg ↑	(2,3) Cu ↑ Mg ↑		
	F	7	(1,2)	(3) Cu ↑ (4,5) Pb ↑	(6,7) Cu ↑ Pb ↑		
Mental Retardation	M	6	(1)	(2) Mg ↑ (3) Pb ↑	(4) Cu ↑ Pb ↑ (5) Cu ↑ Mg ↑	(7) Cu ↑ Zn ↑ Pb ↑	
	F	1	(1)				
Seizure Disorders	M	3		(1) Mg ↑	(2) Cu ↑ Pb ↑		(3) Cu ↑ Zn ↓ Mg ↑ Pb ↑
	F	4	(1)	(2,3) Pb ↑	(4) Cu ↑ Pb ↑		

## DISCUSSION

Contrary to expectations<sup>2</sup> (see introduction), blood copper levels for the depressives group of patients were significantly higher than those found previously<sup>10</sup> for normals (Table I & II). In fact, no patient had a low level and 13 (7 males and 6 females) of the 31 (41.9%) had raised levels. Males had significantly higher zinc levels than females as in normals, but only females had the expected lower levels than normals, as in the literature<sup>2</sup>. Two males and two females had low levels but one male had a raised level (Tables III & IV). There was no significant difference from normals in blood magnesium levels although 4 males had the expected raised levels (Table V & VI) as in the literature<sup>4</sup>. Blood lead levels were significantly higher for females than males, which was the opposite in the controls, but only female patients had higher levels than the corresponding controls. Among the patients, only 2 males (13.4%) but 6 females (37.3%), a total of 8 (25.8%) had abnormal levels whereas in the controls there were 10 males (30.3%) and only 3 females (10.3%) or 21.0% of the 62 subjects. The seven patients with mental retardation had significantly higher blood copper levels than normals, three of them having raised levels. Zinc and magnesium levels were not significantly different from normals, lower levels of the former being expected, according to previous reports<sup>2</sup>. No one had a low zinc level; in fact, one had a raised level. Two had raised magnesium levels. Although 3 males had abnormal blood lead levels, overall, levels were not significantly different from controls. The seven seizure disorders patients had significantly higher copper levels, as in the literature<sup>2</sup>, three having raised levels.

However, levels of zinc and magnesium were not significantly different from normals as previously reported<sup>2,4</sup>. No individual had the expected raised zinc level and, in fact, one had a low level. Two had raised magnesium levels and not one had the expected low level. Blood lead levels were significantly higher than for controls, with 2 males and 3 females (71.4% of patients) being abnormal. The intermetallic correlation coefficient (r, Table VIII) was significant for magnesium versus copper for male depressives and for zinc V. copper for seizure disorders. Also of note was the fact that for zinc V. copper it was positive for depressives (both sexes) and in seizure disorders, whereas for male normals<sup>10</sup> and in previous reports<sup>12</sup> the coefficient was negative. Consideration of the results on a more individual patient basis (Table IX) reveals that among the patients suffering from depression two of three females in the depressive phase of manic depressive illness had the expected metal abnormalities but one had a raised copper level in disagreement with the literature concerning depression<sup>2</sup>. One of two males with schizophrenia with depression had a low zinc level as in previous reports<sup>3,4</sup>, but one male with psychomotor retardation had a raised copper level. Two females had no metal abnormality. The remainder of the depressives had either not been admitted to the wards or had discharged themselves before a diagnosis had been completed and were therefore categorised according to their presenting conditions or manifestations. Six males and two females exhibited according to their presenting conditions or manifestations. Six males and two females exhibited lethargy, lack of interest and/or headaches. All except two of the males had metal abnormalities, the two females and three of the males having metal abnormalities which included raised copper levels. One of the males had raised magnesium (expected<sup>4</sup>) and raised zinc levels (unexpected<sup>2</sup>) in addition. One female, in addition to a raised blood copper level, had a lead level of 74.7 ug/dl. Two of three male and one of two female agitated depressives had no metal abnormality. However, the remaining male had raised copper and zinc levels and the female a lead level of 290.3 ug/dl. Three males and seven females were quiet, withdrawn or suffered from weeping spells. Two of the females had no metal abnormalities, but the other patients had abnormalities including two males and three females with raised copper levels and one male with a low magnesium level (unexpected<sup>4</sup>). A total of 21 of the 31 patients in the depressives group (67.7%) had at least one metal abnormality but only seven of these (33.3% of abnormal cases or 22.6% of the total number of patients) had abnormalities totally in agreement with reports in the literature<sup>2-4</sup>. Of those with mental retardation one out of six males and the only female had no abnormality and, of note, one male had raised blood copper, zinc and lead levels, that of zinc being unexpected, for mental retardation. In all, five (71.4%) of the seven patients had at least one metal abnormality. Three males and four females were having seizure disorders. One female had no metal abnormality and out of the remainder one male had a raised magnesium level and another, had raised copper, magnesium and lead levels and a low zinc level. The magnesium and zinc results were contrary to previous reports concerning seizure disorders<sup>2,4</sup>. Two females had lead levels of 53.7 and 74.7 ug/dl. In all, six of the seven patients (83.7%) had at least one metal abnormality of which four (66.7% of abnormal cases or 57.1% of the total) had results agreeing with the literature. In summary, psychiatric disease is accompanied by blood metal abnormalities and many of our results, especially for blood copper levels in depressives are contrary to those previously reported<sup>24</sup>. As yet we do not know which is the cause and which the effect. One metal abnormality can cause another<sup>13</sup>, which may be happening here in some cases, and it is known that lead is often taken up more readily and has more serious results in those in low socioeconomic groups<sup>14</sup> such as we have here.

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