Original Article

Serum Magnesium Concentration in Patients with Leukemia and Lymphoma

Wafa M. Merza* **MSc**
Ali Y. majid** **FICMS**
Munaf S. Daoud*** **PhD**
Ali M. Jawad**** **PhD**

Fac Med Baghdad 2009; Vol.51, No1
Received May, 2008
Accepted Oct., 2008

Summary:

Background: Leukemias and lymphomas are malignant disorders that occur in the blood forming organs and lymphoid tissue respectively. They are classified to types and several subtypes such as acute or chronic, lymphocytic or myelocytic and T-cell or B-cell lymphocytic for leukemias and histologically into Hodgkin's and Non-Hodgkin's for lymphomas. Literatures do not contain many research work on magnesium in patients with these disorders, although this mineral is essential for many metabolic, enzymic, regulatory and immune reactions in the human body. Therefore, the present study was aimed to evaluate the level of magnesium in the sera of patients with different types of leukemia and lymphoma.

Patients and Methods: Fifty five patients with leukemia and lymphoma and twenty five healthy controls were studied. The patients were attendants of Baghdad Teaching Hospital and Pediatric Teaching Hospital from September 2006 to January 2007. The diagnosis was confirmed by examination of both peripheral blood, lymph node biopsy and/or bone marrow examination. Patients were categorized according to French-American-British Criteria. Thirty five patients with ALL, one with CLL, six with AML, three with CML, three with HL and seven with NHL. Venous blood was collected from each patient or control person and sera were obtained by centrifugation. S[Mg] was measured by Atomic Absorption Flame Spectrophotometry.

Results: The Mean ± SD of S[Mg] in mg/dl of all types of leukemic and lymphomatous patients was lower than the controls. There was a high statistically significant difference ($P<0.01$) in patients with ALL and significant difference ($P<0.05$) in patients with AML and NHL and non-significant difference ($P>0.05$) in patients with CML and HL, compared with the control. Total patients group showed high significant difference ($P<0.01$) compared with control group. The mean distribution of S[Mg] among total patients indicated decreased (58.2%), normal (38.2%) and increased (3.6%) levels.

Conclusion: The present study disclosed the existence of normal to decreased level of S[Mg] in patients with leukemia and lymphoma suggesting an influence of many variable factors. Although the decreased S[Mg] was statistically significant, it was still within lower normal range.

Keywords: Leukemia, Lymphoma serum Magnesium

Introduction:

Leukemia is a condition in which the bone marrow is replaced by a malignant clone of lymphocytic or granulocytic cells which replace the normal hemopoietic cell lines. They affect their normal function producing the clinical features of the diseases which include anemia, bleeding tendency, and increased liability for infections (1). The course of the disease may be chronic or acute. if left untreated, all leukemias are fatal (1). Leukemia is classified, apart from acute and chronic to lymphocytic or myelocytic type according to type of cells of origin. They are further classified to subtypes of each line according to morphological factor under the French-American-British group recommendation (2).

**Dept. of Basic Science, College of Dentistry, Baghdad University.*
*** Consultation Center, Specialized Surgical Hospital.*
****Dept. of Physiological Chemistry, College of Medicine – Baghdad.*
*****Dept. of Medicine in Baghdad Teaching Hospital, College of Medicine – Baghdad*

Lymphomas are disorders caused by malignant proliferations of lymphocytes which accumulate in the lymph nodes causing lymphadenopathy. They may also be found in peripheral blood or infiltrate organs. Lymphomas are classified histologically into Hodgkin's and Non-Hodgkin's (3).

The different types of leukemias and lymphomas were studied extensively trying to solve their etiology which was an enigma before (4). Nevertheless, the literatures do not include many research works on magnesium in patients with leukemia and lymphoma. Magnesium is the wonder element that is a cofactor for many metabolic enzymatic reactions in the body, either as an integral part of a metalloenzyme or as an activator. It has essential roles in the regulation of cell growth, division and differentiation (5). This second major intracellular cation (after potassium) is also effective on several steps in immune reactions (6). Investigators had shown that cellular immune deficiency, thymic atrophy and lymphoma were developed in magnesium-

deficient rodents (7). Another study suggested an association between the deficiency of magnesium and the development of malignant disorder of acute lymphoblastic leukemia and lymphoma (8).
Studies on the magnesium contents and hypomagnesemia in patients with lymphoblastic and lymphocytic leukemia (9, 10, 11, 12) and myeloblastic leukemia (13, 14) were also reported. Although the biological and biochemical importance of magnesium ions are well-understood, the role of this cation in clinical medicine is sometimes overlooked. Therefore, the present study was aimed to estimate the level of magnesium in the sera of patients with different types of leukemia and lymphoma.

Patients and Methods:
Fifty five patients with leukemia and lymphoma and 25 healthy controls were studied. The patients were attendants of Baghdad Teaching Hospital and Pediatric Teaching Hospital from September 2006 to January 2007. The diagnosis was confirmed by examination of both peripheral blood, lymph node biopsy and/or bone marrow examination. The patients were categorized according to French-American-British Criteria. Thirty five patients were with Acute Lymphocytic Leukemia (ALL), one with Chronic Lymphocytic Leukemia (CLL), six with Acute Myelogenous Leukemia (CML), three with Hodgkin's Lymphoma (HL) and seven with Non-Hodgkin's Lymphoma (NHL). Treatment options included supportive measures such as transfusion of packed red cells, platelets, cryoprecipitate, antibiotics and many cytotoxic drugs and also prednisolone or dexamethasone according to treatment protocols.
Three milliliters of venous blood were collected from each patient or control person by venipuncture using disposable syringes. Blood was put in a disposable plastic tube and left to stand out at room temperature for not less than 15 minutes. Tubes were then centrifuged and sera were separated immediately using a disposable pipette. Hemolyzed samples were not used. The serum samples were diluted 1:50 with lanthanum chloride solution to exclude the effect of serum phosphate. A standard solution of 1000 ppm was diluted with deionized water. The working standards of magnesium were prepared by dilution from the stock solution using deionized water to give the following concentration of the working standards (0.5, 1.0, 1.5, 2.0, 2.5, 3.0 and 3.5 mg/dl of magnesium). The magnesium concentration in both patients and control samples were then measured by atomic absorption flame spectrophotometry method. The normal value (reference range) for serum magnesium with this method is 1.45 – 2.75 mg/dl (0.6 – 1.14 mmol/L).
Statistical Analysis:Descriptive statistics included summary statistics of the readings distribution (Mean, Standard Deviation, minimum and maximum). Inferential statistics included matched paired t-test for repeated measurement.
The comparison of significant (P value) in any test were: S□□□□significant difference (P < 0.05),HS = highly significant difference (P < 0.01),NS = non-significant difference (P > 0.05),All statistical analyses were done using Pentium – 4 computer through SPSS program (version - 10).

Results:
The data presented in Table 1 show the Mean ± SD concentration of serum magnesium S[Mg] in mg/dl among groups studied. S[Mg] in the control group (2.09 ± 0.26) was higher than the values of all patients groups ranging (1.62 ± 0.45) to (1.83 ± 0.15) except for CLL group. Statistical analysis of the values of the control with each / total value(s) of the patient group(s) and among the values of the patient groups indicate: A high significant difference in ALL group (P<0.01) compared with the control,A significant difference in AML and NHL groups (P<0.05) compared with the control,A non-significant difference in CML and HL (P>0.05) compared with the control,A non-significant difference (P>0.05) among the groups of patients except for CLL,A high significant difference in total (all) patients group compared with the control (P<0.01).

Table 2 shows the Mean distribution of S[Mg] in mg/dl among types of leukemia and lymphoma. ALL shows (65.7%) decrease, (31.4%) normal and (2.9%) increase in S[Mg]. NHL shows (57.1%) decreased, (28.6%) normal and (14.3%) increased S[Mg]. Total patients shows (58.2%) decreased, (38.2%) normal and (3.6%) increased S[Mg]. Statistical analysis of these values indicats that they are of non-significant difference (P>0.05).

Table 1: Mean Concentration of serum Magnesium (S.Mg) (mg/dl) among groups studied.

Groups	N	Mean of S.Mg (mg/dl)	S.D	Min.	Max.	Comparison of significance	
						P-value	Sig.
Healthy control	25	2.096	0.261	1.7	2.7	-	-
ALL	35	1.623	0.453	0.8	3.5	0.00	HS
CLL	1	0.69	0.00	0.7	0.7	-	-
AML	6	1.737	0.385	1.2	2.1	0.04	S
CML	3	1.833	0.153	1.7	2	0.259	NS
HL	3	1.667	0.153	1.5	1.8	0.067	NS
NHL	7	1.757	0.404	1.2	3.5	0.039	S
Total	80						
Total patients	55	1.649	0.43	0.7	3.5	0.00	HS

N = number of individuals

Table 2: Mean distribution of serum Magnesium (S.Mg) level (mg/dl) among types of leukemia and lymphoma

Types of leukemia		Serum magnesium (S.Mg) (mg/dl)			Total	Comparison of significance	
		Decreased	Normal	Increased		P-value	Sig
ALL	N	23	11	1	35	0.413	Non Sig (P<0.05)
	%	65.7	31.4	2.9	100		
CLL	N	1	0	0	1		
	%	100	0	0	100		
AML	N	3	3	0	6		
	%	50	50	0	100		
CML	N	0	3	0	3		
	%	0	100	0	100		
HL	N	1	2	0	3		
	%	33.3	66.7	0	100		
NHL	N	4	2	1	7		
	%	57.1	28.6	14.3	100		
Total	N	32	21	2	55		
	%	58.2	38.2	3.6	100		

N = number of individuals

Discussion:

The results presented in Table 1 and Table 2 indicate that there is a decreased serum magnesium concentration (S[Mg]) in large percentage (58.2%) of total patients group with leukemia and lymphoma compared to the control group. This decreased level (1.64 ± 0.43 mg/dl) cannot be regarded as a case of hypomagnesemia, which is only considered when the S[Mg] is less than 1.2 mg/dl (0.5 mmol/L). Normally, magnesium deficiency is unlikely since Mg is present in most common foodstuffs and low dietary intake of Mg are associated with general nutritional insufficiency. Symptomatic magnesium deficiency can be attributed to several reasons like dietary insufficiency accompanied by intestinal malabsorption or treatment of certain patients with drugs like diuretics, cytotoxics and immunosuppressants. The results on decreased S[Mg] can be attributed to the cytotoxic drugs used in the treatment protocols. Therapy with cytotoxic drugs may have impaired renal tubular reabsorption of Mg causing its loss in urine. It is well known that the major excretory route of Mg is via the kidneys and about 65% of glomerular filtered Mg is reabsorbed in the loop of Henle. This finding is in consistent with that of Sahin *et al* (8) which suggested an association between the deficiency of this element and the development of malignant disorders. It is also coincided with previous reports of Guo *et al* (9), Sikora *et al* (10), Athanossiadou *et al* (11), Orhun *et al* (12), Tatetsu *et al* (13).

It should be pointed out that although values of S[Mg] are decreased, they are still within the low reference range (Table 1). This does not abolish the existence of intracellular [Mg] depletion. Clearly our values represented extracellular fluid [Mg] i.e. serum [Mg] and this may not reflect the true state of body's reserves particular in chronic disorders.

Other tests have been advocated (e.g. erythrocyte [Mg], muscle [Mg], hair [Mg], Mg loading tests), but all were out of the question in this research work. NMR spectroscopy is one of the techniques that may be used to detect "free Mg^{2+} inside the cells and direct determination of Mg^{2+} in peripheral blood white cells or in muscle biopsy samples.

The decreased S[Mg] in ALL patients (65.7%) can be explained in accordance with the findings of Sahin *et al* (8) and Orhun *et al* (12). A high prevalence of chronic magnesium deficiency in T-cell lymphoblastic leukemia in children with ALL and lymphoma was recorded (8). Moreover, Guo et al (9) reported that hypomagnesemia was a result of movement of extracellular Mg into the skeleton through bone formation after initiation of treatment for ALL (9).

The normal S[Mg] shown in Table 2 and indicated by (38.2%) of total patients is in accordance with the observation made by Sahin *et al* (8). It was reported that S[Mg] in group of patients did not significantly differ from those in the control group.

Other workers had also reported similar findings on the normal and decreased S[Mg] in patients with malignant disorders Halton *et al* (15); Atkinson *et al* (16) and Milionis *et al* (17) showed a controversial results that may have been related to the fact that S[Mg] are not always stable and may be affected by variable factors. Thus, measurement of hair [Mg] seems to be a better indicator in the detection of its chronic deficiency as recorded by Sahin *et al* (8) and Donma *et al* (18).

The increased S[Mg] represented as 3.6% in ALL and NHL patients and to values of 3.5 mg/dl (1.46 mmol/L) are cases of hypermagnesemia. Conditions that interfere with the glomerular filtration (e.g. Renal glomerular dysfunction) result in the retention of Mg and hence elevation of serum level (19).

Further work on the measurement of urine [Mg] would be valuable in distinguishing renal losses of Mg from other causes of hypomagnesemia.

Conclusion:

The present study disclosed the existence of normal to decreased level of S[Mg] in patients with leukemia and lymphoma suggesting an influence of many variable factors. Although the decreased level of S[Mg] was statistically significant, it was still within lower normal range.

References:

1. Wyngaarde, N.; Smith, Bennett: Cecil Textbook of Medicine, 933-955, 1992.

2. Braunwald, Isselbarcher, Petersdorf, Witson Martin, Harrison's Principles of Internal Medicine, 10th Edition, 743, 1985.

3. Christopher R.W., Ian A.D. eds. Davidson's: Principles and Practice of Medicine, 779-780, 18th Ed., 1999.

4. Lichtman, M.A; Beutler, E; Kipps, T.J.; Seligsohn, U.; Kaughausky, K. and Prchal, J.T. Williams Hematology, 7th Ed., McGraw Hill Medical,2006.

5. Vernon, W.B. The role of magnesium in nucleic acid and protein metabolism. Magnesium (1988), 7, 234-248.

6. Galland, L: Magnesium and immune function: An overview. Maganini (1988), 7, 290-299.

7. Hass, G.M.; Galt, R.M; Laing, G.H.; Coogan, P.S.; Magnesium R.O.; Friese, J.A. Induction of a rat T-cell lymphoma-leukemia by magnesium-deficiency – A study of fetal defense against maternal neoplasia. Magnesium (1989), 8, 45-55.

8. Sahin, G.; Erten, U; Duru, F.; Biraen, D.; Kuksek, N.: High prevalence of chronic magnesium deficiency in children with acute lymphoblastic leukemia and malignant lymphoma. Leuk. Lymphoma, (2000), 39(5-6): 555-62.

9. Guo, C.Y.; Halton, J.M.; Barr, R.D.; Atkinson, S.A.: Hypomagnesemia associated with chemotherapy in patients treated for acute lymphoblastic leukemia: Possible mechanisms. Oncol. Rep. (2004), 11(1): 185-9.

10. Sikora, P.; Borzecka, H.; Kollatad, B.; Majewski, M.; Wieczorkiewicz-Plaza, A.; Zajaczkawska, M.: The diagnosis of familial hypomagnesemia with hypercalciuria and dad. nephrocalcinosis in a girl with acute lymphoblastic leukemia case report. Pol Merkur Lekarski. (2006), 20(118): 430-2.

11. Athanossiadou, F., Tragiannidis, A.; Rousso, I.; Katsos, G.; Sidi, V., Koliouskas, D.; Papastergious, T.I. Evaluation of bone metabolism in children with acute lymphoblastic leukemia after induction chemotherapy treatment. Pediatr. Hematol. Oncol. (2005), 22(4): 285-9.

12. Orhun Canbolat; Mustafa Kavutcu and Ilker Durak: Magnesium contents of leukemic lymphocytes. Biometals J. (1994), 7(4): 313-315.

13. Tatetsu, H.; Asou, N.; Nakamura, M.: Torsades de pointes upon fluconazole administration in a patient with acute myeloblastic leukemia. Am J. Hematol (2006), 81(6): 366-9.

14. Kwabota, H.; Anzai, N.; Masutani, H.; Hishita, T: Mg^{2+} or Mn^{2+} dependent endonuclease activities of human myeloid leukemia cells capable of producing nucleosomal-Siza DNA fragmentation. Biochem. Biophy. Res. Commun. (1997), 233(1): 133-8.

15. Halton, J.M.; Atkinson, S.A.; Fraher, l., Webber, C.E.; Cockshott, W.P.; Tam, C; Barr, R.D. Mineral homeostasis and bone mass at diagnosis in children with acute lymphoblastic leukemia. J. Pediatr. (1995), 26: 557-564.

16. Atkinson, S.A.; Halton, J.M.; Bradley, C.; Wu, B.; Barr, R.D. Bone and mineral abnormalities in acute childhood lymphoblastic leukemia: Influence of disease, drugs and nutrition. Int. J. Cancer Supp (1998), 11: 35-39.

17. Milionis, H.J.; Bourantas, C.L.; Siamopoulas, K.C.; Elisaf, M.S. Acid-base and electrolyte abnormalities in patients with acute leukemia. Am. J. Hematol (1999), 62: 201-207.

18. Donma, O.; Gunbey, S.; Tas, M.A.; Donma, M.M. Zinc, Copper and Magnesium concentrations in hair of children from Southeastern Turkey. Biol. Trace Elem. Res (1990), 24: 39-48.

19. Whitby, L.G.; Smith, A.F. and Beckett, G.J.: Lecture notes on Clinical Chemistry, 272, 4th ed. Blackwell Scientific, 1988.