The Turkish Journal of Pediatrics
Volume 23, No. 4, October-December 1981

SERUM CALCIUM AND PHOSPHORUS LEVELS IN CHILDHOOD LIVER CIRRHOSIS*

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Key words: childhood cirrhosis, serum calcium level, serum phosphorus level

The occurrence of hypomagnesemia in cirrhotic children was previously shown by Kaya and Özsoylu[1]. The close relation between the serum magnesium and calcium levels in vitamin D-deficiency rickets was also indicated for the first time by a study at Hacettepe University Institute of Child Health[2]. The first hydroxylation of vitamin D (25-hydroxylation) occurs in the microsomal fraction of hepatocytes, which might be affected in liver cirrhosis[3]. The derangement of the absorption and 25-hydroxylation of vitamin D are both suspected of decreasing calcium absorption and consequently the serum calcium level[3-5]. The serum calcium level is also somewhat related to the serum albumin level, usually found to be decreased in liver cirrhosis[6]. We therefore thought it would be worthwhile to evaluate the serum calcium and phosphorus levels and correlate them to the above factors in cirrhotic children.

Material and Methods

The files of 70 children with cirrhosis diagnosed by biopsy for whom serum calcium (Ca) and phosphorus (P) values were available, formed the material of this study. In addition to the above determinations, total serum protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (AAT), alkaline phoshatase and chloride values were recorded for most of the patients. The results of all tests were available for 51 cases. The ages of the patients ranged from 9 months to 17 years; 17 of them were girls.

The control group was formed of 20 children aged 9 months to 3 years, chosen from the well-baby clinic at Hacettepe Children's Hospital. All were shown by clinical, x-ray and laboratory examinations to be free of bone, kidney, liver and parathyroid diseases. All the laboratory tests were performed by routine methods in the hospital's laboratory.

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Results

Ca values for the 70 patients of the study group ranged from 7.5 mg/dl to 11.3 mg/dl, with a mean of 9.46 ± 0.92 mg/dl; 18 of the patients had Ca values below 9 mg/dl. As the mean of the controls was 9.66 ± 0.62 mg/dl (ranging from 9 to 11 mg/dl), the difference between the controls and the study group was not found to be significant ($p > 0.05$, Table I).

Since protein values can influence serum Ca, the total protein and albumin determinations of the study group were evaluated. Total serum proteins in 12 of the 70 patients were below 6 g/dl while albumin in 30 of them was below 4 g/dl. Seven out of the 12 patients (58%) with hypoproteinemia (< 6 g/dl) and 11 of 58 (19%) with normal protein levels (⩾ 6 g/dl) had hypocalcemia (< 9mg/dl). The mean Ca values of these groups (8.89 ± 1.54 and 9.64 ± 0.05, respectively) were found to differ significantly ($p < 0.01$). Hypoalbuminemia (< 4 g/dl) was present in 30 patients, 12 of whom (40%) had hypocalcemia (< 9 mg/dl). Only 6 of the 40 patients (15%) with normal albumin levels (⩾ 4 g/dl) had hypocalcemia. The statistical evaluation of calcium values in these two groups (mean ± SD: 9.16 ± 1.01 and 9.79 ± 0.16, respectively) also differed significantly ($p < 0.001$, Table II). When the total protein values of the patients were compared on the basis of their calcium levels, the total protein values of 18 hypocalcemic patients were found to be significantly lower than those of the 52 normocalcemic patients ($p < 0.01$). When this comparison was made for the albumin values, the difference between the values of the 18 hypocalcemic patients ($\bar{X}$: 3.48 ± 1.32 g/dl) and those of the 52 normocalcemic patients ($\bar{X}$: 4.35 ± 1.25 g/dl) was more significant ($p < 0.001$, Table III).

The AST levels, available for 68 patients, were found to be high (> 50 U) in 52 (76.5%). The AST levels of 18 patients with hypocalcemia (< 9 mg/dl) ranged from 14 to 2500 U, with a mean of 214 ± 210. The difference between these values and those of 52 normocalcemic patients (whose mean value was 189 ± 204, with a range of 29 to 750 U) was barely significant ($p < 0.05$). The means of the AAT values for these groups were 142 ± 259 and 157 ± 230 respectively, which were not significantly different ($p > 0.05$, Table IV). Alkaline phosphatase values of the patients (as one liver function test) were also evaluated. The mean value of the 18 hypocalcemics was 12.49 ± 6.74 BU, not significantly different from the mean value of 51 normocalcemics (11.56 ± 10.6 U, Table V).

The inorganic phosphorus values ranged from 1.6 mg/dl to 7.4 mg/dl, with a mean of 4.78 ± 1.635 mg/dl, not differing statistically from that of the controls (5.29 ± 0.66 mg/dl; $p > 0.05$, Table VI). But hypophosphatemia (< 4 mg/dl) was detected in 21 (30%) of the patients. Although it was observed more often (8 out of 18; 44.5%) in hypocalcemics (< 9 mg/dl) than in normocalcemics (13 out of 52; 25%), the difference between them was not statistically significant (Table VII).

TABLE I

CALCIUM VALUES OF CIRRHOTICS COMPARED TO CONTROLS (mg/dl)

	Cirrhotics	Controls
Number	70	20
Range	7.5 – 11.3*	9 – 11
$\bar{X}$ ± SD	9.46 ± 0.92	9.66 ± 0.62

* Hypocalcemia (< 9 mg/dl) was observed in 18 patients (25%).

TABLE II

EVALUATION OF Ca VALUES IN CIRRHOTIC CHILDREN IN RELATION TO TOTAL PROTEIN AND ALBUMIN

	Total Protein	
	< 6 g/dl	⩾ 6 g/dl
Number	12	58
Range	7.5 – 10.2	7.5 – 11.3
Ca (mg/dl)		
$\bar{X}$ ± SD	8.89 ± 1.54	9.64 ± 0.05
	p < 0.001	
Hypocalcemia (< 9 mg/dl)	7 (58%)	11 (19%)

	Albumin	
	< 4 g/dl	⩾ 4 g/dl
Number	30	40
Range	7.5 – 10.4	7.9 – 11.3
Ca (mg/dl)		
$\bar{X}$ ± SD	9.16 ±1.01	9.79 ± 0.16
	p < 0.001	
Hypocalcemia (< 9 mg/dl)	12 (40%)	6 (15%)

TABLE III

EVALUATION OF PROTEIN AND ALBUMIN VALUES IN CIRRHOTIC CHILDREN IN RELATION TO CALCIUM LEVELS

	Ca Level	
	< 9 mg/dl	⩾ 9 mg/dl
Number	18	52
Range	4.4 — 8.2	4.6 — 8.9
Protein (g/dl) $\bar{X} \pm SD$	6.177 ± 0.2844	7.177 ± 0.96
	$p < 0.01$	
Hypoproteinemia (< 6 g/dl)	7 (38.9%)	6 (11.5%)
Number	18	52
Range	1.4 — 5.1	2.6 — 6.1
Albumin (g/dl) $\bar{X} \pm SD$	3.48 ± 1.32	4.35 ± 1.25
	$p < 0.001$	
Hypoalbuminemia (< 4 g/dl)	12 (66.6%)	18 (34.6%)

TABLE IV

SERUM Ca, AST AND AAT IN CHILDREN WITH CIRRHOSIS

	Ca < 9 mg/dl	Ca ⩾ 9 mg/dl
Number	18	50
Range	14 — 2500 U	29 — 750 U
AST $\bar{X} \pm SD$	214 ± 210	189 ± 204
	$p < 0.05$	
Elevated AST (> 50 U)	13 (72.22%)	39 (78%)
Number	18	50
Range	15 — 1300 U	11 — 1070 U
AAT $\bar{X} \pm SD$	142 ± 259	157 ± 230
	$p > 0.05$	
Elevated AAT (> 50 U)	10 (55.5%)	27 (54%)

TABLE V

ALKALINE PHOSPHATASE VALUES OF CIRRHOTIC CHILDREN

	Ca < 9 mg/dl	Ca ⩾ 9 mg/dl
Number	18	51
Range	3.3 – 44	2.5 – 42.4
$\bar{X}$ ± SD	12.49 ± 6.74	11.56 ± 10.6
	p > 0.05	
Elevated alkaline phosphatase (> 15 U)	5 (27.8%)	11 (21.57%)

TABLE VI

INORGANIC P VALUES OF CIRRHOTIC CHILDREN COMPARED TO CONTROLS' (mg/dl)

	Cirrhotics	Controls
Number	70	20
Range	1.6 – 7.4	4 – 6.5
$\bar{X}$ ± SD	4.78 ± 1.635	5.29 ± 0.66
	p > 0.05.	

TABLE VII

EVALUATION OF INORGANIC P VALUES IN CIRRHOTIC CHILDREN RELATED TO THEIR Ca LEVELS

	Ca Level	
	< 9 mg/dl	⩾ 9 mg/dl
Number	18	52
Range	1.6 – 7.2	2.5 – 7.4
P (mg/dl) $\bar{X}$ ± S.D.	4.62 ± 1.587	4.84 ± 1.2923
	p > 0.05	
Hypophosphatemia (< 4 mg/dl)	8 (44.5%)	13 (25%)

Since vitamin D levels could not be determined in all patients, the chloride-phosphate ratios of 51 patients were evaluated as an indirect evidence of parathormone levels, which would be elevated in rickets. The mean value of the study group was 24.62 ± 10.11, significantly higher ($p < 0.01$) than that of the control group (18.96 ± 0.42). However, the serum calcium levels did not show any correlation with the chloride-phosphate ratios, which ranged from 14 to 46.

Discussion

Rickets in chronic hepatobiliary diseases of infants is known to occur where serum Ca and P levels are affected[7]. The pathogenesis of this kind of rickets has been studied recently[8-10]. Low serum 25-hydroxyvitamin D (25-OHD) levels have also been shown in most adults with hepatitis, liver cirrhosis and cholestatic liver disease[11]. Meyer et al[5] found decreased levels of serum 25-OHD in 23 adults with liver cirrhosis in whom hypocalcemia and hypophosphatemia were also detected, but they did not believe that the two findings were correlated. Serum 25-OHD levels could be determined in only 4 of our patients and were found to be low in all (3.65 to 5.26 mg/dl).

Although hypocalcemia and hypophosphatemia were detected in 25% and 30% of our patients respectively, the values of the study group were not significantly different from those of the controls. Hypocalcemia was observed significantly more often in patients with hypoproteinemia and hypoalbuminemia. However, the reverse was also observed: hypoproteinemia and especially hypoalbuminemia were found more often in hypocalcemics than in normocalcemics. We believe that the Ca levels of our patients were more influenced by the total protein and albumin levels than by the other parameters studied. Since most of the serum calcium is bound to albumin, which is synthesized by the liver, the derangement of albumin synthesis in this disease could be one of the most important factors in the reduction of the calcium level. The fact that AST values were observed to be slightly higher in hypocalcemics might be accepted as a reflection of the disease's activity, in which case hypoalbuminemia might occur more often. Since hypophosphatemia was also not significant in children with cirrhosis, the effect of hypovitaminosis D in the pathogenesis of hypocalcemia in our patients is less likely, even though it was present in the four cases which could be studied. But obvious rickets was not shown in any of the patients by radiologic examination of the wrist. The chloride-phosphate ratio was found to be over 35, which was believed to result from the combined actions of parathormone on renal handling[12] in only 6 cases; the calcium and alkaline phosphatase levels of these 6 cases were also found to be similar to the rest. Therefore, we could not find any evidence that the low calcium of the study group related to rickets. Contrary to the observations of Meyer et al[5] concerning adults, we could

not show that the calcium levels were significantly decreased in cirrhotic children even though hypocalcemia was more often observed in them. It is our belief that in the presence of hypocalcemia in cirrhotic children, serum protein levels and especially albumin should be evaluated.

Summary

Low serum calcium (< 9 mg/dl) and inorganic phosphorus (< 4 mg/dl) levels were detected in 25% and 30% respectively of patients with cirrhosis. Hypocalcemia was present more significantly in patients with hypoalbuminemia. Hypophosphatemia was observed more often in hypocalcemic cirrhotics (44.5%) than in normocalcemics. Although hypovitaminosis D was shown in 4 patients, obvious rickets was not present in any of our cases by x-ray examination of the wrists.

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