ORIGINAL REPORT

Prevalence of Vitamin D Deficiency and Rickets in Children with Cholestasis in Iran

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Abstract- This study was aimed to determine prevalence of Vitamin D deficiency and rickets in children with cholestatic liver diseases. Forty eight children with established cholestatic liver disease who referred to gastrointestinal clinic of Children Medical Center (Tehran, Iran) between April 2010 and March 2011 were enrolled in a cross-sectional study. Laboratory analysis including calcium, phosphate, albumin, total and direct bilirubin, aminotransferases, alkalinephosphatase (ALP), prothrombin time (PT), parathyroid hormone (PTH), total protein determined by routine laboratory techniques. Mean age of participants was 299.1 ± 676.8 days (range 2-3600 days) whereas twenty one were female (43.8%) and 27 (56.3%) were male. Twenty two (45.8%) had evidences of rickets in X-ray evaluation. Three children with rickets and two with normal X-ray had Vitamin D deficiency while ten in rickets group and 16 in normal group had Vitamin D insufficiency. The main underlying diseases were anatomical biliary atresia in cases with rickets and idiopathic in other group. Rickets and Vitamin D deficiency should be considered in chronic cholestatic children.

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Keywords: Rickets; Vitamin D; Chronic cholestasis; Children

Introduction

Prolonged intra and extra hepatic bile ducts injuries in children as a result of inflammatory, autoimmune, and metabolic disorders (such as galactosemia, tyrosenemia) may cause cholestatic liver disease (1). One of the complications of chronic liver diseases is osteodystrophy which is reported in 9-83% of cases (2-6) due to mal-absorption of fat-soluble vitamins like vitamin D (7-10). Vitamin D which is essential for bone metabolism is converted to 25-hydroxyvitamin D (25[OH]D) in the liver and then converted into 1,25-dihydroxyvitamin D in the kidney to be metabolically active. In this way, liver and kidney play key roles in activation of vitamin D (11).

Previous findings showed low bone mineral density and radiologic evidence for rickets and osteopenia and high prevalence of fractures in children with cholestatic liver diseases (11-12). Treatment by calcium and vitamin D supplements or liver transplantation in severe cases is reported to improved bone disease in children (13,14). Early detection and appropriate treatment will improve prognosis in such cases. The aim of this study was to determine prevalence of vitamin D deficiency and rickets in children with cholestatic liver diseases in Iran.

Materials and Methods

Forty eight children with established cholestatic liver diseases who referred to gastrointestinal clinic of Children Medical Center (Affiliated hospital of Tehran University of Medical Sciences, TUMS) between April 2010 and March 2011 were enrolled in this cross-sectional study. All parents asked to fill informed consent forms although study had been approved by Ethical committee of TUMS.

Laboratory analysis including calcium, phosphate, albumin, total and direct bilirubin, aminotransferases, alkalinephosphatase (ALP), prothrombin time (PT),

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parathyroid hormone (PTH), total protein and 25-hydroxyvitamin D (25[OH]D) determined by routine laboratory techniques.

The serum calcium level was corrected for albumin concentration. Left wrist X-ray applied for rickets diagnosis.

Statistical analyses were performed with a statistical software package (SPSS version 16). Data are presented as mean values and SDs. Student's t-test for continuous variables and the Pearson Chi-square test with the Fisher's exact test for categorical variables applied for between group assessments. *P*-value less than 0.05 was considered statistically significant

25[OH]D level less than 10 nM considered as deficiency, levels between 10-29 nM supposed as insufficiency and between 30-100 nM presumed as sufficient.

Results

Mean age of participants was 299.1 ± 676.8 days (range 2-3600 days) whereas twenty one were female (43.8%) and 27 (56.3%) were male. Twenty two (45.8%) had evidences of rickets in X-ray. Table 1 shows laboratory findings of all cases.

Three children with rickets and two with normal X-ray had vitamin D deficiency, ten in rickets group and 16 in normal group had Vitamin D insufficiency (Table 3).

Table 1. Laboratory findings of all cases.

	Mean ± SD	**Normal ranges**
Calcium (mM)	9.2 ± 0.7	8.6-10.3
Phosphate (mM)	4.7 ± 1.5	> 14 years: 2.7-4.5 <14 years 4.7-6.7
ALP (U/L)	1425.2 ± 767.1	180-1200
AST (U/L)	436.8 ± 478.3	Up to37
ALT (U/L)	268.1 ± 352.9	Up to40
PT (s)	14 ± 4	Less than 12 seconds
Albumin (g/L)	3.5 ± 0.5	3.8-5.1
T. Bill (µM)	16.8 ± 10.8	0.6-1.4
D. Bill (µM)	8.1 ± 5.5	0.2-0.8
PTH (pM)	35.6 ± 26.9	16-65
25[OH]D (nM)	34.5 ± 32.6	less than 10 nM= deficiency, between 10-29 nM= insufficiency between 30-100 nM= sufficient

Table 2. Comparison laboratory findings between two groups.

	With rickets **Mean ± SD**	**Without rickets** **Mean ± SD**	***P*-value**
Calcium (mM)	9.4 ± 0.6	9.0 ± 0.7	0.1
Phosphate (mM)	4.6 ± 1.4	4.7 ± 1.6	0.9
ALP(U/L)	1554.3 ± 884.3	1315.9 ± 649.8	0.2
AST (U/L)	280.3 ± 199.3	596.1 ± 597.5	0.02
ALT (U/L)	199.6 ± 162.9	326 ± 451.9	0.1
PT (s)	14.7 ± 4.5	13.4 ± 3.6	0.2
Albumin(g/L)	3.6 ± 0.4	3.4 ± 0.6	0.3
T. Bill (µM)	18.9 ± 12.9	15.0 ± 8.4	0.2
D. Bill (µM)	8.9 ± 6.3	7.4 ± 4.6	0.3
PTH (pM)	43.6 ± 32.3	28.6 ± 19.0	0.05
25[OH]D(nM)	35.1 ± 31.3	34.0 ± 34.3	0.9

Table 3. Comparison between Ca, P and 25[OH] vitD in two groups.

	With rickets (%)	Without rickets (%)	*P*-value
25[OH]D deficiency	3(13.6%)	2 (7.6%)	0.5
25[OH]D insufficiency	10(45%)	16(61.5%)	
Normal 25[OH]D	9 (40.9%)	8(30.7%)	
Hypo calcemia	2 (9%)	6 (23%)	0.2
Hyper calcemia	1(4.5%)		
Normal calcium levels	19(86.3%)	20 (76.9%)	
Hypo phosphatemia	1(4.5%)	2 (5.2%)	0.7
Hyper phosphatemia	1(45.4%)	1 (2.6%)	
Normal phosphate	20(50%)	23 (59.8%)	

Table 4. Underlying diseases of cases in both groups.

	With rickets evidence	Without rickets evidence	*P*-value
Metabolic	0	2(7.6%)	0.6
Anatomic	11(50%)	7(26.9%)	
Idiopathic	2(9%)	9(34.6%)	
infectious	0	1(3.8%)	
Storage diseases	0	3(11.5%)	
Endocrine	1(4.5%)	0	
PFIC	6(27%)	1(3.8%)	
Others	2(9%)	3(11.5%)	

Four cases with evidence of rickets and one with normal pattern had elevated PTH (0.1).

Discussion

To our knowledge this is the first study for determining vitamin D deficiency and rickets in children with cholestatic liver diseases in Iran. Osteodystrophy as a complication of chronic liver diseases in children is a consequence of mal-absorption of vitamin D and disturbance of calcium/phosphorous balance. There is no exact treatment for this condition although liver transplantation and calcium/vitamin D supplements are introduced to support bone formations (15). Previous studies indicated that there is no exact correlation between serum vitamin D level and incidence of rickets in children with chronic liver diseases [13]. Our results showed that calcium and vitamin D levels are not significantly different in children with or without rickets. This can be indicative of the role of other factors in bone formation in children with cholestasis. D'Antiga *et al*. reported significant increase in bone density and height of children who underwent liver transplantation after one year (16). Increase in protein anabolism, decrease in portal hypertension, better absorption of fat-soluble vitamins like vitamin D are benefits of liver transplantation (16).

We found significant difference in only alanine aminotransferase enzymes between two groups. Taveira *et al.* reported higher alanine aminotransferase and alkaline phosphatase in a total of 13 children with chronic cholestatic disease than 22 control subjects (17).

Bilirubin contents were similar in children with and without evidence of rickets in current study, although previous studies suggested that hyperbilirubinemia is associated with osteoblast proliferative capacity inhibition which results in hepatic osteodystrophy (18,19).

Hypocalcemian and vitamin D deficiency are associated with low bone density and osteoporosis which are associated with mortality, morbidity and quality of life impairment (20). Fractures (as results of low bone mass) are also associated with an excess mortality. Bone mineral density is the best way to assess bone minerals and endocrine system but it is costly and time consuming. Laboratory tests (calcium, phosphate, ALP) can give valuable information on the metabolic status of the bone which are accessible and easy to apply (20).

In current survey, calcium, phosphate and ALP levels were not different significantly between patients with and without rickets. In a study by Bucuvalas *et al.* eight of nine children with cholestatic liver disease had normal plasma biochemical marker and only one case had normal BMD (bone mineral density) while radiologic findings were normal in all of the cases (21). In conclusion, we can suggest that vitamin D and bone mineral screening should be considered in children with chronic cholestatic diseases.

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