Profile of the causes of symptomatizing hypocalcemia in infants and children

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Background
Symptomatizing hypocalcemia is defined as reduction in the level of ionized calcium in the blood to less than 0.95 mmol/l, associated with obvious manifestations such as neuromuscular impairment in the form of convulsion, carpopedal spasm, paresthesia or stridor, etc. Calcium hemostasis, to keep the level of calcium maintained at normal level, is controlled by normal nutritional intake of vitamin D and calcium-containing foods, by normal calcium and vitamin D absorption from the intestine, by normal-synthesis of vitamin D by the liver and kidneys, and by the effect of the normal-parathyroid gland. The main aim of the work was to give a profile of the causes of symptomatizing hypocalcemia in infants and children presenting to Assiut University Children Hospital.

Patients and methods
The study included 50 patients aged 2 months to 17 years (IRB#17100552). Besides full clinical assessment, all cases had the following investigations done: CBC, kidney and liver function test, serum calcium, alkaline phosphatase, vitamin D, and parathyroid hormone level measured. The chest radiography and wrist radiography were done in all cases. Intestinal biopsy was performed where indicated.

Results
Nutritional vitamin D-deficiency rickets was present in 62% of the cases, hepatic rickets was encountered in 6% of the cases, celiac disease was encountered in 8% of the cases, hypoparathyroidism was present in 4% of the cases, cow's milk allergy was present in 2% of the cases, and hypocalcemia secondary to antiepileptic drugs was present in 4% of the cases.

Conclusion
Vitamin D supplementation should be recommended during infancy and adolescence, where periods of rapid growth of bone occur. Good advice must be given to parents about foods rich in vitamin D and calcium.

Keywords:
calcium, carpopedal spasm, hypocalcemia, rickets, vitamin D deficiency, vitamin D

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Introduction

Symptomatic hypocalcemia means hypocalcemia manifested by obvious and manifest symptoms such as seizure, stridor, bronchospasm, or manifest tetany [1].

Calcium hemostasis is maintained by normal calcium absorption from the intestine, and this may be impaired by the presence of intestinal villous atrophy as in cases with celiac disease, poor renal or liver functions with lack of synthesis of alpha-hydroxycholecalciferol synthesized by the liver or in cases with severe insufficient vitamin D and/or the calcium in the diet. Furthermore, vitamin D-dependent hypocalcemia occurs when there is failure of tissue vitamin D receptors in spite of normal vitamin D intake. Similarly, hypoparathyroidism may be a cause of symptomatizing hypocalcemia [2].

It is interesting to note that low vitamin D in the blood, besides being a cause of symptomatizing hypocalcemia, has been associated with occurrence of repeated infections secondary to lack of both chemotactic and phagocytic capability of the macrophages, decreased differentiation and proliferation of immune globulins production by the β cells, and enhancement in their apoptosis. Furthermore, there is a link between vitamin D deficiency and muscle tone, and therefore pot belly and postural kyphosis. In addition to hypocalcemia, hypotonia owing to vitamin D deficiency occurs, and this is because 125-dihydroxycholecalciferol is present in the nucleus and plasma membrane of mammalian skeletal muscles, where it modulates muscle cell calcium exchange as well as cellular calcium [3].

Patients and methods

The study included 50 patients with symptomatizing hypocalcemia. There were 29 males and 21 females (IRB#17100552). Their ages ranged from 2 months to 17 years. Besides full clinical history and accurate examination, all cases had the following investigations done: serum calcium, P, alkaline phosphatase (ALP), renal and liver function test, as well as vitamin D and parathyroid hormone (PTH) levels. All cases had chest radiography, wrist radiography, and abdominal ultrasonography done.

Ethics approval and consent to participate: this study was approved by the Committee of Medical Ethics of Faculty of Medicine Assiut University. Before beginning of the process, written informed consents were taken from parents with explanation of benefits of the study, risks expected, and suggested treatment for each case.

Statistical analysis

Statistical analysis was done for the data obtained using SPSS (Statistical Package for the Social Sciences, version 23, IBM Corp., and Armonk, New York, USA). Nominal data were expressed in the form of frequency (percentage).

Results

Our results are shown in Tables 1–3.

The study included 50 cases with symptomatic hypocalcemia. There were 29 males and 21 females. Their ages ranged from 2 months to 17 years.

The study included 50 cases with symptomatic hypocalcemia: 31 (62%) cases had nutritional vitamin D-deficiency rickets; seven (14%) cases had renal symptomatizing hypocalcemia, where five (10%) of them were on renal dialysis; malabsorption was seen in four cases; symptomatic hypocalcemia was reported in three (6%) cases with liver disease; in one case, cow's milk allergy was encountered; cases on antiepileptic therapy (Tegretol and oxcarbazepine) constituted two children; and hypoparathyroidism was present in two (4%) cases.

Among cases with vitamin D-deficiency nutritional rickets, 15 (48.4%) had active rickets. Healing rickets was present in 16 (51.6%) cases.

Phosphorous was high in 20 (40%) cases, low in two (4%) cases, and normal in the rest of cases (56%).

Table 1 demographic data of the studied cases (*n*=50)

Demographic data	Symptomatic hypocalcemia (*n*=50)
Age (years)	*n* (%)
<1	33 (66)
1-5	11 (22)
>5	6 (12)
Sex	
Male	29 (58)
Female	21 (42)

Table 2 The distribution of the causes of symptomatic hypocalcemia in the studied cases (*n*=50)

Causes of symptomatic hypocalcemia (*N*=50)	*n* (%)
Nutritional vitamin D	31 (62)
Active rickets	15 (48.4)
Healing rickets	16 (51.6)
Renal	7 (14)
Malabsorption (celiac)	4 (8)
Liver disease	3 (6)
Antiepileptic	2 (4)
Hypoparathyroidism	2 (4)
Cow's milk allergy	1 (2)

Table 3 The laboratory results of the studied cases (*N*=50)

	n (%)
Level of phosphorous (*n*=50)	
Normal	28 (56)
High	20 (40)
Low	2 (4)
Level of vitamin D (*n*=50)	*n* (%)
Normal	12 (24)
Low	38 (76)
The prevalence of raised parathyroid hormone (*n*=50)	*n* (%)
High	48 (96)
Low	2 (4)

Vitamin D level was low in 76% of cases and normal in the rest of cases (24%).

It was observed that raised PTH was present in 48 of the cases (96%) and low in the rest of cases (4%).

Discussion

Whether rickets is active or healing, a shortage of vitamin D causes disruptions in the metabolism of bone minerals, which affects bone deposition and mineralization. Additionally, a lack of vitamin D results in a reduction in intestinal calcium absorption, which in turn causes a drop in blood calcium levels, stimulation of the parathyroid gland to release PTH, mobilization of calcium from the bones into the blood, defective bone mineralization, and a reduction in blood phosphorous levels owing to excretion in the urine. Given this, vitamin D supplementation should not be started until after intravenous and oral calcium therapy have been administered and the calcium level

has returned to normal. This is done to prevent the recurrence of hypocalcemia symptoms like tetany.

In reality, fibroblast growth factor 23, which controls how phosphate is handled by the kidneys, is produced by bone, which is regarded as an endocrine organ. As children's bone growth and turnover rates are high, symptoms of hypocalcemia are more common in this age range.

Furthermore, these young children receive inadequate amounts of vitamin D from breast milk and unfortified fresh cow's milk. The fact that these newborns are being scrubbed, the glass of the windows being closed, and the air being dusty all prevent UV rays from reaching and penetrating the skin of these younger children.

Without treatment with calcium and vitamin D, the parathyroid gland becomes tired and subsequently develops hypoparathyroidism after the natural compensatory hyperparathyroidism fails. The biochemical alterations of symptomatic hypocalcemia include low P and elevated ALP.

In the current study, renal and hepatic rickets each occurred in 14 and 6% of the cases, respectively. This is in agreement with Migliaco *et al.* [4], who explained that not only because the diseased liver does not produce 1,25-dihydroxycholecalciferol but also because the bile salts are decreased, which reduces vitamin D absorption, and because the diseased liver produces fewer vitamin D binding proteins. On the contrary, Liu *et al.* [5] linked renal osteodystrophy and increased blood creatinine to occurrences of renal rickets in people with hypocalcemia that manifested as symptoms and a glomerular filtration rate of less than 30 ml/min. In this regard, our results are consistent. In actuality, renal dialysis was being used in our patients with renal symptomatizing hypocalcemia.

In a study done by Teaema and Al Ansari [6], the authors reported a case series of 19 newborn infants presented with symptomatic hypocalcemia in a 2-year period only. Vitamin D deficiency in both the infants and their mothers was the attributed cause in all studied patients. Of the 19 patients, nine had an associated unexpected response of PTH, which might be explained by immature calcium–vitamin D–PTH axis at this early age or by scarcity of calcium salts in their bones; the low ALP in this group of patients might favor the first.

Similar findings were reported by Ashraf *et al.* [7]. No overt clinical findings of rickets were reported in our series, which can be explained by the short duration of mineral deficiency, even before radiological findings can occur.

In 4% of our cases, there was medication convulsion secondary to antiepileptic medication. This concurs with Arora *et al.* [8], who suggested that these medications work by reducing calcitriol production and that calcitriol production is also typical in renal failure.

Recommendation

(1) Vitamin D supplementation should be recommended during infancy and adolescence where periods of rapid bone growth occurs.
(2) Further big studies should be done with laboratory estimation of vitamin D level regularly to establish the policy of vitamin D and calcium supplementation, especially with the increasing use of junk food or delivery foods in both rural and urban areas.
(3) Encouragement of rearing chicken at home to obtain their eggs. Egg yolk is a rich source of vitamin D and calcium. Other foods rich in vitamin D such as fish, meat, butter, and liver are expensive.
(4) Infants should be fed up with fresh cow's milk. Although being rich in calcium, yet it is a poor source of vitamin D.

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Conflicts of interest

There are no conflicts of interest.

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