ORIGINAL REPORT

A Cross-Sectional Study to Determine the Prevalence of Calcium Metabolic Disorder in Malignant Childhood Cancers in Patients Admitted to the Pediatric Ward of Vali-Asr Hospital

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Abstract- Calcium metabolic disorders, such as hypercalcemia is a potentially life-threatening disorder especially when coupled with an already compromised condition. The aim of this study was to determine the prevalence of metabolic calcium disorders in childhood cancers of patients admitted to the pediatric ward of Vali-Asr Hospital from the year 2001-2008. The study was carried out by reviewing hospital records of these patients from the hospital archives. Range of age was between 1 and 18 years. Inclusion criteria for the study population were the presence of total serum calcium evaluated at least once; and for the hypercalcemia subgroup, at least two occasions of elevated calcium levels. The prevalence of hypercalcemia and other metabolic abnormalities of phosphorus, alkaline phosphatase, urea and creatinine; the prevalence of parameters such as age, gender, type and duration of cancer were determined within these groups. Median of elevated calcium levels was also determined to classify hypercalcemia into moderate and severe hypercalcemia. Median was 11.7 mg/dl, therefore, severe hypercalcemia was ≥11.7mg/dl and moderate hypercalcemia, a range between the upper limit of normal, 10.8 and 10.2 mg/dl for the child and adolescent respectively, and 11.7 mg/dl. Relationship between hypercalcemia and the other metabolic disorders and parameters were analyzed by the SPSS V.17 program. The population of study consisted of 148 cases. Hypercalcemia was found in 8 (5.4%) patients. Half of the cases were associated with severe hypercalcemia and acute lymphoblastic leukemia (ALL). Out of 148 cases, there were 92 (62%) boys and 56 (38%) girls. Mean and median ages were 10.9 and 11 years respectively. Mean duration of cancer was 12.8 and median 6 months. There were 57 (38.5%) cases of leukemia and 91 (61.5%) cases of solid tumors. The most common cancers were ALL, 44 cases (29.7%) followed by brain tumors, 19 cases (12.8%); non-Hodgkin's lymphoma, 16 cases (10.8%); 13 cases of acute myeloid leukemia (AML) (8.8%); 13 cases of Ewing sarcoma (8.8%); osteosarcoma, 9 cases (6.1%); Hodgkin's lymphoma, 6 cases (4.1%); others, 19.1%. There was no significant difference between hypercalcemia and the metabolic disorders and parameters. Metabolic calcium disorder, especially hypercalcemia, is not a rare finding in pediatric cancers. ALL, the commonest pediatric cancer, is most often associated with this disorder.

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Introduction

Cancer in children is overall a rare finding (1). Hematopoietic tumors (leukemia, lymphoma) are the most common childhood cancers, followed by brain/CNS tumors and sarcomas of soft tissue and bone. There is a wide variability in the age-specific incidence of childhood cancers (2). Pediatric cancers differ markedly from adult malignancies in both prognosis and distribution by histology and tumor site (1).

Statistics in the USA shows an incidence rate of 16.5/100 000, representing about 1% (12,400 cases/year)

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of all new cancer cases (1). Malignant neoplasms remain the second most common cause of all deaths (12.7%) among persons 1-14 years of age in the USA (1).

Hypercalcemia of malignancy

Hypercalcemia frequently occurs in adults with a wide variety of solid tumors but is identified much less often in children. It has been reported in infants with malignant rhabdoid tumors of the kidney or congenital mesoblastic nephroma and in children with neuroblastoma, medulloloblastoma, leukemia, Burkitt's lymphoma, dysgerminoma, and rhabdomyosarcoma, though, it has been found that acute lymphoblastic leukemia (ALL) accounts for approximately 50% of this metabolic complication in the pediatric age group and in half of these patients, hypercalcemia is present at diagnosis (3). In the context of malignancy, the etiologic mechanisms are either abnormal secretion of circulating humoral factors or local osteolysis in the case of bone marrow invasion. In the absence of bone marrow invasion, the mechanism is mainly indirect via paraneoplastic secretion of PTH-rP, a peptide possessing a strong homology (70%) with PTH which it shares many biologic effects (4,5). PTH-rP, by its PTH-like action, also increases the tubular resorption of calcium, decreases the renal excretion of phosphorus, and stimulates 1-alpha-hydroxylase, accentuating hypercalcemia. However, not all cases of paraneoplastic hypercalcemia are accompanied by an elevation of PTH-rP. Other circulating factors secreted by tumor cells are also responsible for this elevation of serum calcium: TNF, IL-6, IL-1 alpha, 1 beta, and TGF alpha and beta (6). Rarely, tumors produce active 1, $25(OH)_2$ D or PTH ectopically (1).

Another factor that can be responsible for hypercalcemia is decreased renal excretion of calcium due to decreased glomerular filtration and increased renal tubular absorption of calcium (7,8).

Hypercalcemia is an oncologic emergency with non-specific symptoms that if not recognized early could lead to patient deterioration and organ failure (8). Serum calcium levels greater than 12 mg/dl can cause multiple organ dysfunctions and at levels exceeding 20 mg/dl, can even be fatal (8). The mainstay of the initial treatment is aggressive therapy with normal saline, often in conjunction with a loop diuretic. More significant hypercalcemia requires therapies with glucocorticoids such as prednisone. Calcitonin is used as an adjunct to inhibit bone resorption. Oral or intravenous biphosphonates also inhibit bone resorption through their effects on osteoclasts (1,7). In some cases only specific anti cancer treatment and/or hemodialysis yields resolution (1,7).

Other metabolic abnormalities

Tumor lysis syndrome is a triad of hyperuricemia, hyperkalemia, hyperphosphatemia with secondary hypocalcemia.

Materials and Methods

Study population and data collection

A cross-sectional study was used to determine the prevalence of metabolic calcium disorders, mainly hypercalcemia, in malignant childhood cancers by collecting and reviewing hospital folders of these patients from the hospital archives. Range of age was between 1 and 18 years old.

Patients that had a laboratory record of at least one total serum calcium level evaluated at anytime during their illness met the inclusion criteria of our study group.

Inclusion criteria for the hypercalcemia subgroup were those patients with at least two episodes of elevated total serum calcium levels, of which for each patient a mean was calculated and from the entire number of cases, a median value determined. The latter used to classify hypercalcemia into moderate and severe hypercalcemia.

Other metabolic disorders of phosphorus, alkaline phosphatase (ALP), blood urea nitrogen (BUN) and creatinine were determined based on the patient's age and/or gender; the prevalence of prednisolone and aluminum hydroxide use for treatment; the prevalence and distribution of age, gender and type of cancer were also determined within the study group.

The prevalence of each variable/parameters mentioned above and the relationship between them and hypercalcemia was also analyzed within the hypercalcemia subgroup.

Statistical analysis

Statistical analysis was done by the Statistical Package for the Social Sciences (SPSS-version 17). Significance values were evaluated by Fisher's exact test and independent sample t-tests. *P*-value was significant if less than 0.05.

Results

Study group consisted of 148 cases. There were 92 (62%) boys and 56 (38%) girls (Figure 1). Mean and median of age were 10.9 (Std. deviation 4.3) and 11

years respectively. Mean duration of cancer was 12.8 months (Std. deviation 15.7mo) and median 6 months. There were 57 (38.5%) cases of leukemia and 91 (61.5%) cases of solid tumors (all tumors but leukemia) (Figure 2). The commonest cancer was ALL, 44 cases (29.7%), followed by brain tumors, 19 cases (12.8%); non-Hodgkin's lymphoma, 16 cases (10.8%); 13 cases (8.8%) each of acute myeloid leukemia (AML) and Ewing sarcoma; osteosarcoma, 9 cases (6.1%) (Figure 3). The prevalence of metabolic disorders, hypercalcemia, hypophosphatemia and hyperphosphatemia, elevated ALP, BUN and creatinine levels, use of prednisolone and aluminum hydroxide for treatment were also determined in the study group (Table 1).

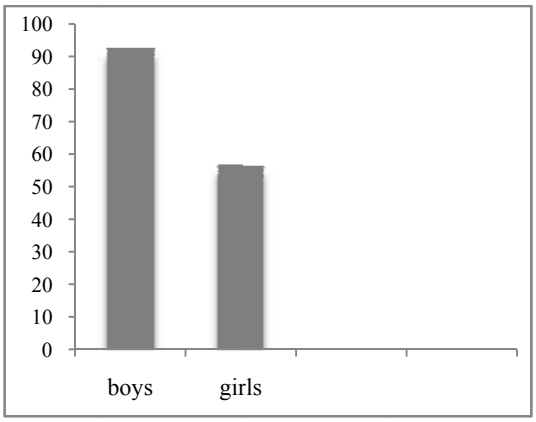

Figure 1. Gender distribution of cancer

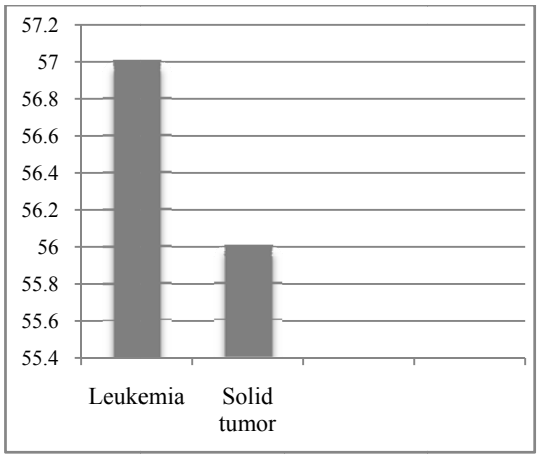

Figure 2. Classification of cancers into leukemia and solid tumors

Table 1. Prevalence of metabolic abnormalities in the studied group

Variable	No of cases	Cases in %
Hypocalcemia	19	12.8
Hyperphosphatemia	14	9.5
Hypophosphatemia	22	14.9
Elevated ALP	29	19.6
Decreased ALP	0	0
Elevated BUN	13	8.8
Decreased BUN	0	0
Elevated creatinine	10	6.8

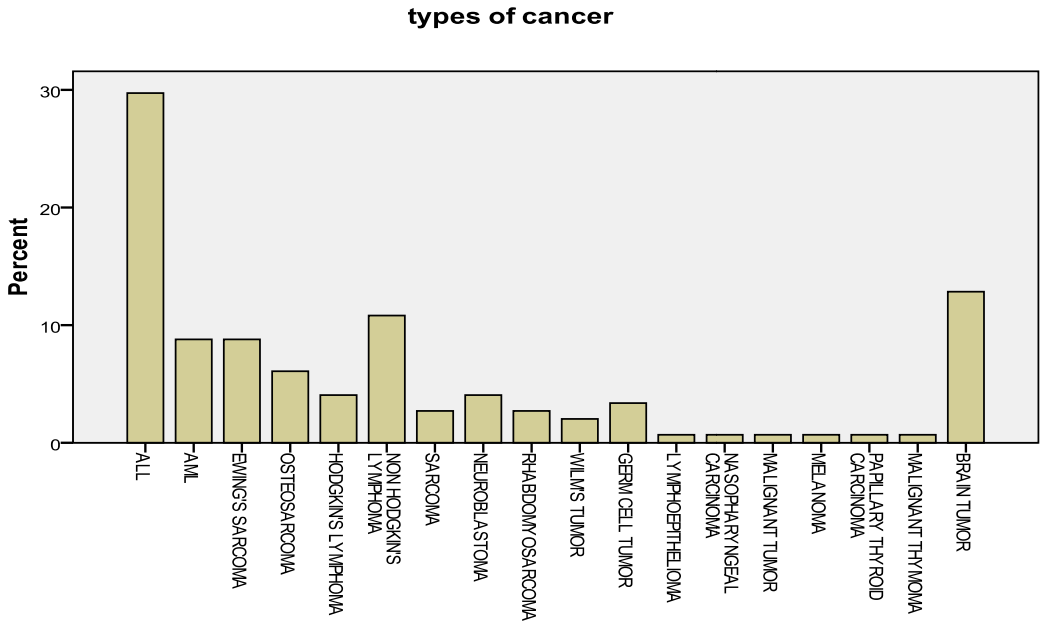

Figure 3. Prevalence of the different cancers

Table 2. Types of cancer and hypercalcemia

Type of cancer	No of cases	Severe hypercalcemia [Ca≥11.7 mg/dl]	Moderate hypercalcemia [Ca<11.7 mg/dl]	Percent age of cases
ALL	4	3	1	50%
NHL	2	1	1	25%
RMS	1	-	1	12.5%
ES	1	-	1	12.5%
Total	8	4	4	100%

NHL: Non-Hodgkin's lymphoma, RMS: Rhabdomyosarcoma, ES: Ewing sarcoma

Table 3. Hypercalcemia compared with other metabolic disorders

	Phosphorus		ALP		BUN		Creatinine	
	Elevated	Normal	Elevated	Normal	Elevated	Normal	Elevated	Normal
Moderate hypercalcemia [Ca<11.7 mg/dl] (No. of cases)	2	2	1	3	0	4	0	4
Severe hypercalcemia [Ca≥11.7 mg/dl] (No. of cases)	2	2	0	4	2	2	2	2
Total	4	4	1	7	2	6	2	6
Total (%)	50	50	12.5	87.5	25	75	25	75

Prednisolone was used for treatment in 46 cases (31.1%) and aluminum hydroxide in only 2 cases (1.4%). Hypercalcemia was found in 8 (5.4%) out of the 148 cases. Seven out of the 8 cases were boys. Four Patients had moderate hypercalcemia (Ca<11.7 mg/dl) and the four others, severe hypercalcemia (Ca ≥11.7 mg/dl). Half of the cases, 50% were associated with leukemia. Three cases of ALL had severe and 1 case moderate hypercalcemia (Table 2).

The coexistence of hypercalcemia and other metabolic disorders is displayed on Table 3.

Prednisolone was used for treating hypercalcemia in 3 cases (2 cases of severe and 1 case of moderate hypercalcemia) and aluminum hydroxide in 1 case of severe hypercalcemia.

Results of statistical analysis between hypercalcemia and the variables/parameters are displayed on Tables 4 and 5. *P*-value <0.05 was regarded as significant.

Table 4. Determining significance values between hypercalcemia and metabolic disorders

	Variable	*P*-value
Hypercalcemia	Phosphorus	1.000
	ALP	1.000
	BUN	0.429
	Creatinine	0.429

Table 5. Determining significance values between hypercalcemia and the parameters

	Variable	*P*-value
Hypercalcemia	Age	0.950b
	Gender	1.000a
	Type of cancer	0.657a
	Duration of cancer	0.900b

a *P*-value is determined by Fisher's exact test

b *P*-value is determined by t-test

Discussion

Hypercalcemia of malignancy is the most common life-threatening metabolic complication with a prevalence of about 5-20% in the adult population. In childhood cancers it is equally as life-threatening but not as common (8). According to the study of McKay *et al.*, over a period of 29 years, 25 out of 6,055 children treated for cancer were identified with hypercalcemia (0.4%) (8). Kerdudo *et al.*, over a period of 7 years found 16 cases of hypercalcemia and reported a prevalence of 1.3% (9).

In this study that involved 148 cases of malignant childhood cancers over a period of 7 years, a prevalence of 5.4% (8 cases) was discovered; indicating that hypercalcemia in childhood malignancies is not so rare after all. Leblanc *et al.* carried out a large series which

identified 17 (0.7%) out of 2,400 cases of solid tumors with hypercalcemia, and also reported this finding to certainly constitute an underestimation because calcium levels were not obtained in all the children (10). This was also the case in our study, because not all of the cancer patients had their calcium levels evaluated. This could both have led to an over or underestimation of the true prevalence of hypercalcemia.

Half of the hypercalcemia cases were associated with ALL. This is consistent with the research of McKay *et al.,* in which acute leukemia comprised the majority of the 25 cases of hypercalcemia (8). The other cases of hypercalcemia was seen in non-Hodgkin's lymphoma (2 cases), and in a case of Ewing's sarcoma and rhabdomyosarcoma.

In this study, there were two cases of concurrent hyperphosphatemia and renal impairment (defined as elevated creatinine and BUN levels) in the severe hypercalcemia subclass. In the study of McKay *et al.,* acute renal failure was found in 2 patients, one of which was due to hypercalcemia and the other from tumor lysis syndrome of which after the event of the latter, hypercalcemia resolved on its own (8). Mild increases in serum creatinine due to volume depletion from hypercalcemia-induced polyuria and poor intake are not uncommon in hypercalcemia of malignancy (11,12).

Although unspecific, but elevated ALP may indicate bone activity, bone or liver cancer/metastasis, kidney disease, and in certain cancers used as a tumor or prognostic marker (13). Only one case among our hypercalcemia subgroup had an elevated ALP level.

Prednisolone, a synthetic corticosteroid well known for its anti-inflammatory properties also possesses anti cancer action, inhibits extrarenal activity of 1-alpha hydroxylase and decreases intestinal absorption of calcium. It is used as a second line agent to treat hypercalcemia (1,9). Only 3 of our cases were on treatment with prednisolone during their episode of hypercalcemia. This finding cannot be proven that prednisolone was solely used for its anti-hypercalcemic effect at that time though and could have been administered for its other properties. In the study of McKay *et al.,* they report the resolution of hypercalcemia in a patient that was receiving prednisone only as part of her chemotherapy protocol (8). Aluminum hydroxide is an intestinal chelator of phosphorus used to treat hyperphosphatemia (14). Only one of the patients with severe hypercalcemia and concurrent hyperphosphatemia was administered this drug. Another patient with normal calcium and phosphorus levels was also administered aluminum hydroxide. Statistical analysis to determine the relationship between hypercalcemia and the other metabolic disorders and parameters: hyperphosphatemia, elevated ALP, BUN, creatinine; age, gender and duration of cancer showed no significant difference (P>0.05). Kawasaki *et al*., reported to be no significant trend detected based on age, gender, primary site and pathologic type in the development of hypercalcemia in patients with rhabdomyosarcoma (15).

Out of the 148 cases there was a male predominance for cancer, 92 boys versus 56 girls, similar to the findings of most researches that have reported the male gender to possess greater risks for developing cancer (1). Solid tumors were more than the leukemia in this study, but the commonest cancer was acute lymphoblastic leukemia, contributing to about a third of the entire cases (16). This is consistent with the findings of McKay *et al.,* where out of 6,055 cases, solid tumors composed of more than half of their cases, yet ALL was the most common malignancy among them (8). The second most common cancer as stated in textbooks are brain tumors followed by non-Hodgkin's lymphoma, Ewing's sarcoma, osteosarcoma and Hodgkin's lymphoma (1). In this study, and in descending order: brain tumors, Non-Hodgkin's lymphoma, AML and Ewing's sarcoma were also common.

Within the study group, hypophosphatemia was a greater finding compared to hyperphosphatemia. Hypophosphatemia could have been caused by the use drugs (aluminum hydroxide or bicarbonate, like that found in antacid MOM), low magnesium levels, vitamin D deficiency, kidney dysfunction, endocrine problems, etc. Hyperphosphatemia, one of the components of tumor lysis syndrome, may develop following chemotherapy especially in the setting of inadequate renal function. It has also been reported, but unusually, that hypocalcemia can occur as a lethal complication of cytolytic therapy. Occasionally, hyperuricemia and hyperphosphatemia with secondary hypocalcemia are frequently encountered at diagnosis, even before chemotherapy is initiated in patients with T cell or B cell ALL or B cell precursor leukemia with high leukemic cell burden (12). Elevated BUN and creatinine levels, indicating renal impairment, occurred almost simultaneously in our study (13 and 10 cases respectively). Acute renal failure is a well recognized complication in patients with lymphoproliferative disorders (17). Thirty one percent of the cancer patients were treated with prednisolone indicating that the latter may have been used mainly for its anti-cancer rather than its anti-hypercalcemic effects. As a very unpopular

drug discovered in our study was aluminum hydroxide which was only used in 2 cases. The presence of these metabolic abnormalities indicates that closer attention needs to be paid to these abnormalities especially before initiating chemotherapy. In conclusion, metabolic calcium disorder, hypercalcemia, in pediatric cancers is not a rare condition and must be corrected especially prior to induction chemotherapy. Acute leukemia is the commonest pediatric cancer and is most often associated with hypercalcemia; therefore awareness to this finding and its proper management is mandatory. We recommend that future studies aim to determine the etiology of hypercalcemia per case and in order to determine the true incidence of hypercalcemia, measurement of total serum calcium levels in all cancer patients, with or without symptoms/signs be added to regular workup protocols.

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