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Changing Pattern of Hypercalcemia in a Hospital Setting – A Hospital Based Experience

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ABSTRACT

Background: Hypercalcemia is a common metabolic abnormality of varying severity that can be adequately diagnosed and treated. Primary hyperparathyroidism and malignant neoplasms are responsible for >90% of all cases. **Objectives:** To study the clinical presentation and etiological profile of hypercalcemic patients at a district level hospital over a period of 24 months. The number of patients of hypercalcemia due to other rare cause like vitamin D intoxication have been increasing mainly due to over the counter supplementation. **Methods:** Forty patients, 22 males with a mean age of 50±10.2 and 18 females with mean age 45±7.6 with hypercalcemia were studied. The first step in evaluating hypercalcemia was confirming it first, with an initial evaluation including the measurement of intact parathyroid hormone , 25-hydroxy vitamin D levels and alongwith imaging wherever required. **Results:** Out of 40 patients studied, the most common clinical presentations were symptoms of aches and pains in 12 patients and incidental finding of hypercalcemia in 10 patients, altered sensorium in 6 patients. In etiological profile, the most common etiology was vitamin D intoxication in 10 patients followed by hyperparathyroidism in 9 patients and malignanacy in 7 patients respectively. **Conclusion:** In our study vitamin D intoxication (VDI) was the most common cause of hypercalcemia. as compared with multiple studies previously which showed malignancy and hyperparathyroidism as predominant causes. Inadvertent excessive use of pharmaceutical preparations is the most common etiology of exogenous vitamin D toxicity.

Keywords: Hypercalcemia, Hyperparathyroidism.

INTRODUCTION

Hypercalcemia is a relatively common condition in hospital populations. The most common reasons for hypercalcemia in any hospital setting are malignancies, followed by symptomatic PHPT, granulomatous diseases and other uncommon causes. The advent of rapid and reliable automated methods for measuring serum calcium makes it possible to detect hypercalcemia early in the course of the disease process, even when patients are asymptomatic or when patients are evaluated for unrelated conditions. Calcium estimations are made on routine blood analysis in a significant number of patients that are evaluated in our hospital. We intended to look into the profile of hypercalcemia among patients that presented to our hospital and the frequency distribution of its causes in view of recent trends of changing etiology of hypercalcemia.

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MATERIALS AND METHODS

This prospective study was conducted at the district level hospital of Jammu and Kashmir (DH Baramulla). This study included 52 subjects of hypercalcemia studied from June 2017 to may 2019.A proper informed consent was taken before incorporating the subjects into the study. Detailed history, physical examination and laboratory parameters were obtained from the participating study subjects. The hospital measures serum total calcium on an automated analyzer (Roche Hitachi 912 Chemistry Analyzer, Boehringer Mannheim, Germany). Serum calcium was analyzed using 0-cresolphthalein dye-binding technique. Serum 25-hydroxy vitamin D (25OHD) and intact parathyroid hormone (iPTH) levels were measured by the electro-chemiluminescence immunoassay (ECLIA) on cobase-e411 immunoassay analyzer. The actual number of patients investigated for calcium status was determined. The initial serum calcium done on each patient was used to categorize hypercalcemia (serum total calcium of > 10.4 mg/dL in adults and > 10.8 in children below 5 years of age). All cases were categorized into two groups: (i) transient

hypercalcaemia and (ii) sustained hypercalcaemia. The adjustment to serum albumin was accomplished as shown below.

Corrected serum calcium was derived from the formula: Corrected (Ca) = (0.8 x (normal albumin - patient's albumin) + serum (Ca) level. The frequency distribution of causes was estimated separately in each group. Sustained group was further categorized into PTH-dependent and PTH-independent groups. The PTH-independent group is further sub-classified depending upon the etiologies for hypercalcemia. The data is expressed as numbers, percentages, standard deviations and ranges whichever applicable.

Table 1: Age, Gender distribution, PTH and Vitamin D levels

Age	**Mean ±SD : 50±10.2 (M), 45±7.6 (F)**
Males	22
Females	18
PTH level(pg/ml)	65±32
Vit D level (ng/ml)	90±26
Serum calcium(ng/dl)	14.4±1.8
Phosphate (mg/dl)	3.5±1.5
Albumin (mg/dl)	4.5±1.2

Table 2: Clinical presentation of patients- LBA: Low back ache, LAP: lymphadenopathy

Aches and pains	**12 patients**
Incidental finding	10
Altered sensorium	6
Bony tenderness/pains/LBA	4
Haemoptysis	1
Abdominal pain	1
Fever /LAP	1

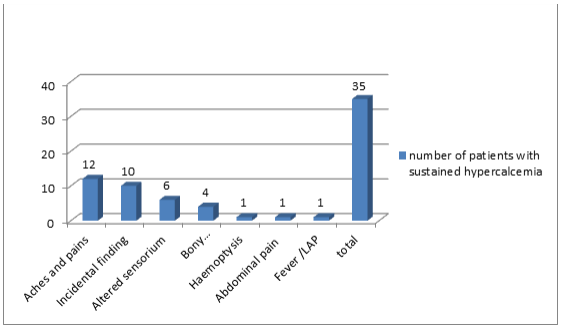


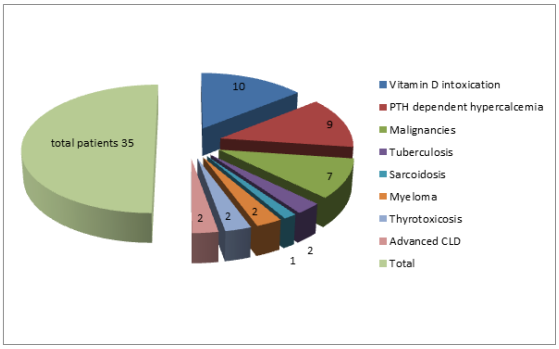
Figure 1: Number of patients with sustained hypercalcemia

Table 3: Etiological profile of hypercalcemia

Etiology	**Number of patients**
Vitamin D intoxication	10
PTH dependent hypercalcemia	9
Malignancies	7
Tuberculosis	2
Sarcoidosis	1
Myeloma	2
Thyrotoxicosis	2
Advanced CLD	2

In this study, a total of 52 subjects were included, out of which 40 patients had complete evaluation. 22 males (mean age 50 ± 10.2) and 18 females (mean age of 45.5±7.6) [Table 1]. The most common clinical presentation was aches and pains in 12 patients, incidental finding in 10 patients, altered sensorium in 6 patients, bony pains and tenderness in 4 patients, hemoptysis in 1 patient, abdominal pain in 1 patient, fever and lymphadenopathy in 1 patient. [Table 2].The most common cause of hypercalcemia in our patients was vitamin D intoxication in 10 patients followed by primary hyperparathyroidism in 9 patients and malignancies{Multiple myeloma, carcinoma lung with bony metastasis, carcinoma breast with bony metastasis and GI malignancy} in 9 patients.[Table 3].

The mean calcium, PTH and vitamin D levels levels in various categories of hypercalcemia has been tabulated in [Table 1].



DISCUSSION

The most common cause of hypercalcemia in our study was vitamin D intoxication as compared to other studies where hyperparathyroidism and malignancies accounted for most of cases (14). Primary hyperparathyroidism and malignancy are the two most common causes of increased serum calcium levels, together accounting for about 90% of all cases (Potts and Jüppner, 2012). Mechanisms associated with hypercalcemia are classically divided into parathyroid hormone and non-parathyroid hormone mediated.

Parathyroid hormone is the main regulator of calcium homeostasis and its primary increased secretion alters the regulation of serum calcium by acting on different target organs (bone, kidney, gut) (Horwitz et al., 2013). Hypercalcemia of non-parathyroid origin is mostly related to production of parathyroid hormone related protein (PTHrP), calcitriol, or cytokines as mediators. Malignancy related hypercalcemia-humoral hypercalcemia of malignancy is a paraneoplastic syndrome resulting from the secretion of parathyroid hormone related protein by the tumour (Shane, 1999). Although any kind of neoplasia may cause the syndrome of humoral hypercalcemia of malignancy, squamous carcinomas are most commonly implicated. Hypercalcemia may be due to local osteolysis, most usually observed in haematological cancers. Overproduction of calcitriol represents the key

mechanism in the development of hypercalcemia associated with some forms of malignancy and with granulomatous diseases. Malignant cells and granulomas can over-express 1-α-hydroxylase and increase the conversion of calcidiol to the active form of vitamin D, calcitriol, leading to increased intestinal absorption of calcium, hypercalciuria, and hypercalcemia (Horwitz et al., 2013).

The literature reports that hypercalcemia due to an overdose of vitamin D may appear if serum levels of 25(OH)D reach a range of 150-200 ng/ml (Gupta et al., 2014). For this reason, it is generally accepted that serum 25(OH)D level above 150 ng/ml should be observed before a diagnosis of vitamin D toxicity(VDT). VDT may be defined as a state when markedly elevated of 25 (OH)D levels (> 150 ng/mL) coinciding with hypercalcemia, hypercalciuria and very low or even undetectable PTH activity. However, the major clinical worries related to VDT most often focus on elevated calcium levels (hypercalcemia) and a variety of nonspecific symptoms (Agraharkar et al., 2012). Vitamin D toxicity involves an increased concentration of vitamin D metabolites reaching the vitamin D receptor (VDR) in the nucleus of target cells and causing exaggerated gene expressions.

Hypercalcemia occurs in up to 30% of patients with malignancy.[5] This is the most common group of hypercalcemia in the hospital setting. The malignancies most commonly associated with hypercalcemia are epidermoid malignancies (squamous cell lung carcinoma, urothelial cancers, head and neck cancers), multiple myeloma, breast cancer, renal cell carcinoma and lymphoma.[6,7] In our study there were 7 cases of malignancy related hypercalcemia-2 cases of carcinoma lung ,2 of breast carcinoma and 2 were GI tract related. In our study in comparison to above mentioned studies, the most common cause of hypercalcemia was vitamin D intoxication possibly explained by over the counter use of vitamin D and improper use by quacks alongwith other supplements and steroid abuse. All cases of Vitamin D toxicity were caused by intramuscular injections over a period of 4 to 6 months. Most of them were treated with fluids, calcium/vitamin D restriction and steroids. In some of them, hypercalcemia persisted for many months. Over years, this group has become important cause of non-parathyroid hypercalcemia in hospital settings.

There were 2 patients with advanced CLD, who developed hypercalcemia in this study. There were no other causes for hypercalcemia except for the liver disease per sé. Hepatic malignancy was ruled out in these patients by appropriate biochemical tests and imaging. Gerhardt et al. described the same pattern of hypercalcemia in 11 patients who had advanced CLD but no hepatic cancer (13). Hypercalcemia caused by advanced CLD without hepatic neoplasia is a poorly understood condition. The unique feature of this type of hypercalcemia is its transient nature that may or may not require treatment.In this study there were 9 cases of PTH dependent hypercalcemia with a changing trend in that there were more of aymptomatic cases picked up early in there course than symptomatic ones. Thyrotoxicosis related hypercalcemia was seen in one graves disease and one TMNG with both having mild hypercalcemia(<12 mg/dl).In under-developed nations, chronic infective granulomatous diseases still contribute significantly to the non-parathyroid group of hypercalcemia,with 2 patients in our series having pulmonary TB and 1 having sarcoidosis.

Limitations: Limited number of patients and data available at secondary care hospital setting cannot be generalized to a larger setting of patients. The incidence of hypercalcemia in our hospital may not be generalized.

CONCLUSION

This 24-month prospective study reveals that the profile of hypercalcemia is changing in hospital care settings. Malignancy-associated hypercalcemia was the largest group previously in any hospital setting. PHPT is changing in that more and more patients are asymptomatic compared to previous studies in developing countries where symptomatic PHPT predominated. Vitamin D toxicosis is not uncommon these days, especially in under-developed nations where parenteral vitamin D preparations are available over-the-counter. Clinicians should be aware of these changing patterns of hypercalcemia in hospital settings.

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