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Research Article

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Unraveling the Mysteries of Hypercalcemic Encephalopathy: A Clinical Experience from A Tertiary Care Center.

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Abstract

Background

Hypercalcemic encephalopathy is a rare but clinically significant condition characterized by a range of complex symptoms due to elevated serum calcium levels. The causes of this condition can stem from various underlying factors, with the most common being primary hyperparathyroidism, malignancies, and granulomatous diseases. This study aims to provide a comprehensive clinical profile of hypercalcemic encephalopathy by examining a cohort of patients presenting at a tertiary care center.

Results

We analyzed etiologies, clinical manifestations, and short-term outcomes in 32 patients with a mean age of 32.45 years. The study revealed that malignancy-related hypercalcemia was the predominant cause in a significant portion of the cases (46.8%), indicating that cancer-associated mechanisms play a substantial role in the development of hypercalcemic encephalopathy. Hyperparathyroidism, accounted for 34.3% of the cases, followed by granulomatous disease, which was the underlying factor in 12.5% of the cases. Unfortunately, six patients experienced mortality during the study. The primary reasons for these unfortunate outcomes were related to hypercalcemia itself, highlighting critical importance of its proper management.

Conclusion

The treatment responses observed in the study provided valuable insights. About 37.5% of the patients responded positively to the administration of intravenous fluids and calcitonin, a hormone involved in calcium regulation. However, for those who did not respond to these standard treatments, the introduction of denosumab, a medication that inhibits bone resorption and can lower calcium levels, yielded positive outcomes. This suggests the potential utility of denosumab in cases where traditional treatments are ineffective.

Overall, this study significantly contributes to our understanding of hypercalcemic encephalopathy by delving into its clinical features, the range of underlying causes, responses to treatment, and patient outcomes. The findings underscore the importance of recognizing this condition promptly and implementing tailored interventions to ensure optimal management and improved patient care

1. Introduction

Hypercalcemia is defined as the serum calcium concentration two standard deviations above the mean values. The normal serum calcium ranges from 8.5 mg/dL-10.5 mg/dl [1]. Calcium homeostasis is primarily controlled by the parathyroid hormone, calcitonin, and vitamin D. Derangements in this process can result in alterations of serum calcium which has adverse bearing on the health of a person [2]. It can cause a variety of symptoms affecting multiple body systems, including the gastrointestinal, renal, cardiac, musculoskeletal, and neurological systems. Approximately 40% of patients with hypercalcemia experience neurological symptoms [3]. The severity of the condition is

often related to the intensity of the symptoms experienced. Mild hypercalcemia, with a calcium level between 10.5-11.9 mg/dL, may cause anxiety or depression. Moderate hypercalcemia, with a calcium level between 12-13.9 mg/dL, can lead to cognitive dysfunction. Severe hypercalcemia, with a calcium level greater than 14 mg/dL, can cause lethargy, confusion, stupor, or even coma [4].

Hypercalcemia is prevalent in various healthcare settings, including primary care, emergency departments, and hospitals. While the majority of cases (around 90%) can be attributed to primary hyperparathyroidism and malignancy, it's essential not to overlook the remaining 10% [3]. A thorough evaluation of this minority group is crucial to ensure comprehensive care. Exploring potential factors such as granulomatous disorders (like sarcoidosis and tuberculosis), vitamin D intoxication, and other underlying conditions is of utmost importance, as these issues may have significant consequences that require further investigation.

Encephalopathy arises from brain dysfunction, resulting in altered consciousness levels or content. It can stem from various factors, including overall brain insults and localized injuries, with underlying causes stemming from neurological or systemic issues [5]. Potential triggers encompass infections, metabolic imbalances, medication side effects, mass effects like tumors, and exposure to radiation. Although metabolic encephalopathies often lead to hospitalization, hypercalcemia is a relatively rare occurrence. Common symptoms encompass confusion, drowsiness, anxiety, cognitive impairments, behavioral changes, and, in severe cases, coma. The intensity and rate of hypercalcemia progression can lead to symptoms ranging from mild drowsiness to coma [6].

Our research aims to comprehensively analyze the clinical and causative aspects of hypercalcemic encephalopathy in patients treated at our advanced care center. Additionally, we analysed the short-term outcomes of these individuals.

2. Materials and Methods

This prospective study was conducted on adult patients (age > 18 years) with hypercalcemia (corrected calcium >10.5mg/dL) diagnosed on two separate occasions at tertiary health care center, from 1st January 2019 to 31st December 2019. A total of 50 patients were enrolled into the study after satisfying the inclusion and exclusion criteria and were followed up for a period of three months. A through clinical history (demographics, symptoms, past medical history, personal history, drug use, and family history) and general examination was carried out on each subject. Thereafter, etiological evaluation was carried out and they were followed up for a period of three months. A provisional diagnosis guided specific investigations, such as serum protein electrophoresis, tissue biopsies and aspiration cytology, parathyroid assays, thyroid profiles, serum ACE and 25 hydroxy Vitamin-D levels. The etiology, clinical presentation, course of treatment, and outcome of each patient with hypercalcemia were assessed. Wherever necessary, appropriate radio-nuclear imagings were performed. Ethical clearence was obtained from Institutional Ethical Clearence of Dayanand Medical College and Hospital, Ludhiana (IRB) The collected data was analyzed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). For quantitative data, the mean and SD were determined, whereas for qualitative variables, proportions and percentages were computed. Using the Student t-test and the ANOVA test, quantitative factors between the study groups were compared. Chi-square test was used to compare categorical data. Statistical significance was defined as a probability value (p-value) less than 0.05.

3. Results

A total of 32 patients were enrolled in the study between 1st January 2019 to 31st December 2019, with confirmed diagnosis of hypercalcemic encephalopathy. The age distribution of the patients ranged from 18 to 83 years with 15.6 % of patients belonging to the age group of 18-40 years, whereas 34.4%, 43.8%, and 6.25% belonged to the age group of 41-60,61-80 and more than 80 years, respectively. A total of 16(50%) of the patients were male and 16(50%) were female. A total of 6 (18.8%) had mild hypercalcemia, whereas 10 (31.2%) and 16 (50%) had moderate and severe hypercalcemia, respectively (Table 1).

Malignancy was the most prevalent underlying etiology of hypercalcemia seen in 15 (46.9%) of patients, followed by primary hyperparathyroidism being etiology in 11 (34.4%). Granulomatous disease and vitamin D toxicity was seen as primary cause of hypercalcemia in 4 (12.5%) and 2 (6.25%) patients. Among patients with malignancy, carcinoma lung was most prevalent (33.3%) followed by carcinoma breast (26.7%), while other malignancies making rest of 60% malignancy patients. 10 (90.9%) patients with primary hyperparathyroidism had underlying parathyroid adenoma while 1 (9.1%) had underlying parathyroid carcinoma. Sarcoidosis comprised 75% of patients with granulomatous disease diagnosis while tuberculosis comprised only 25% of them.

I.V fluids and calcitonin was initial treatment modality that was started on all patients and resulted in resolution of symptoms in 12 (37.5%) patients, involving 7 (21.9%)patients with hyperparathyroidism and 5 (15.6%) patients with malignancy. Among rest of the patients with hyperparathyroidism, 3 were initiated on zoledronic acid and 1 was initiated on denosumab instead of zoledronic acid due to underlying renal failure. Similarly, renal failure was the reason for initiation of denosumab instead of zoledronic acid in 4 patients with malignancy, with rest of 6 being managed on zoledronic acid itself. All the patients with granulomatous disease were initiated on adjuvant steroid therapy. For patients with vitamin D toxicity a steroid were management of choice but couldn't be used in 1 patient because of underlying pancreatitis and was started on zoledronic acid.Time from initiation of treatment to symptom resolution was 8.6 days for maliganancy, 6.7 days for primary hyperparathyroidism, 4.4 days for granulomatous disease and 3.4 for vitamin D toxicity. With average time for treatment initiation to symptom resolution being7.1±1.2 days. (Figure 1).

Out of 32 patients involved in study, mortality was outcome in 6 (18.8%) patients. Majority (83.3%) of patients with mortality had underlying malignancy, while remaining 1 mortality case was due to post operative complication on patient with primary hyperparathyroidism being managed for thyroid adenoma(Table 2 and figure 2).

Parameters	Sub-groups	Hypercalcemia (at admission)						Total	P- value
		Mild (n=6)		Moderate (n=10)		Severe (n=16)			
Age group (in years)	18-40	2	33.33%	2	20%	1	6.25%	5	0.265
	41-60	3	50%	5	50%	3	18.75%	11	
	61-80	1	16.66%	3	30%	10	62.5%	14	
	>80	0	0	0	0	2	12.50%	2	
Gender	Female	2	33.33%	5	50%	9	56.25%	16	0.214
	Male	4	66.67%	5	50%	7	43.75%	16	
Etiology	Malignancy	1	16.66%	4	40%	10	62.5%	15	0.067
	Primary hyperparathyroidism	2	33.33%	4	40%	5	31.75%	11	0.23
	Granulomatous diseases	2	33.33%	1	10%	1	6.25%	4	0.07
	Vitamin D toxicity	1	16.66%	1	10%	0	0	2	0.25

Table 1: Baseline Characteristics of Patients with Hypercalcemic Encephalopathy

Parameters	In Hospital Outcome				Total	Chi- square value	p- value
	Discharge (n=26)		Death (n=6)				
Malignancy	10	38.46%	5	44.4%	15	2.541	0.098
Primary hyperparathyroidism	10	38.46%	1	22.2%	11	3.215	0.452
Granulomatous disease	4	15.38%	0	11.1%	4	2.692	0.442
Vitamin D toxicity	2	7.69%	0	11.1%	2	2.262	0.453

Table 2: Outcomes of The Patient with Hypercalcemic Encephalopathy.

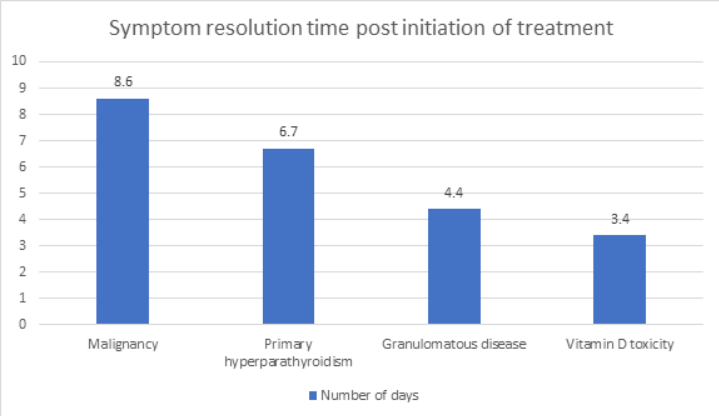

Figure 1: Symptom Resolution Time Post Initiation of Treatment.

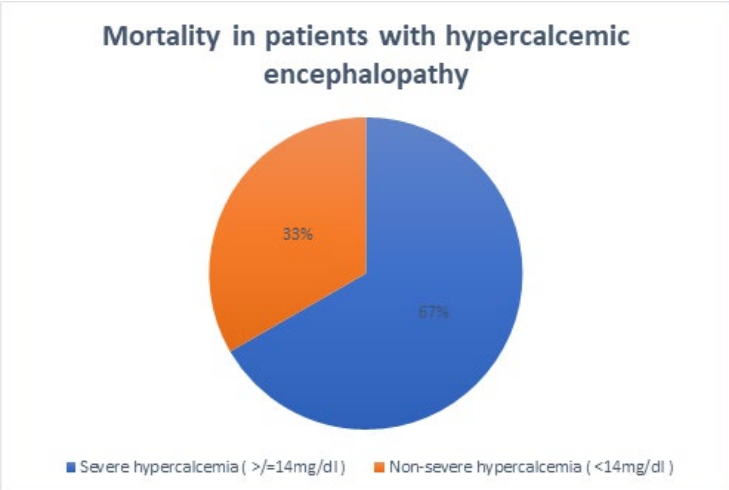

Figure 2: Mortality in Patients with Hypercalcemic Encephalopathy.

4. Discussion

Hypercalcemic encephalopathy, a rare yet potentially life-threatening condition, has long perplexed medical professionals and researchers [4]. This rare entity is characterized by disturbances in calcium homeostasis leading to varied neurological symptoms such as altered mental status, seizures, weakness, tremors, focal neurological deficits, etc. posing a unique challenge in diagnosis and treatment. Due to the rarity and the lack of comprehensive epidemiological studies specifically focused on hypercalcemic encephalopathy, it's challenging to provide a precise prevalence rate and dearth of data on clinical profiling [7].

The present study enrolled 32 patients presenting to a tertiary care center with mean age of 32.45± 4.45 years (age distribution 18 to 82 years) with equal number of males and females. Malignancy related hypercalcemia was the most common etiology (46.8%), followed by hyperparathyroidism (34.3%) and granulomatous disease (12.5%). A total of 6 patients demised during the study with 5 died due to hypercalcemia and one died due to post-parathyroidectomy complications. A total of 37.5% patients responded to intra-venous fluids and clacitonin whereas 5 non-responders, respondedto denosumab. The mean time of clinical response to the treatment was 7.1±1.2 days.

The prevalence of malignancy-related hypercalcemia as the leading etiology highlights the importance of considering hypercalcemia in the context of cancer diagnosis and management. Primary hyperparathyroidism and granulomatous disease were also identified as significant contributors to this condition, emphasizing the need for a comprehensive diagnostic approach to uncover underlying causes.

Cornette M et al decribed 8 patients with hypercalcermicenephalopathy and determined symptoms, neuropsychological anomalies, electroencephalogram (EEG) findings, and the effects of restoring normal blood calcium levels. All the patients had difficulty in maintaining upright posture and difficulty in walking. EEG pattern was characterized by a slow occipitoparietal background activity that is interrupted by high-voltage anterior delta bursts lasting 1 to 4 seconds and may serve as a potential diagnostic marker [7]. However, EEG was not evaluated in our study.

Our study has various strengths as it is the first and the largest study to study the demographic, clinical and outcome factors in hypercalcemic encephalopathy. Moreover, this is the first study to determine its response to various treatment modalities. However, our study has few limitations as it is a single-center study and its implication worldwide needs larger multi-center studies. EEG findings were not recorded during the study which may serve as a potential marker for the diagnosis. Nonetheless, this study forms the basis for a larger study and attracts attention to researchers to this rare entity.

Our findings underscore the importance of recognizing hypercalcemic encephalopathy as a potential complication, particularly when underlying factors such as malignancy, primary hyperparathyroidism, or granulomatous diseases are present. This awareness is crucial for timely diagnosis and effective management, given the wide range of neurological symptoms observed, spanning from mild confusion to profound changes in consciousness. As our understanding of hypercalcemic encephalopathy continues to evolve, further research is warranted to delve into long-term outcomes, optimal treatment strategies, and potential preventive measures. By building upon this foundational knowledge, our aim is to improve patient outcomes, enhance diagnostic precision, and contribute to the growing body of evidence in the field of hypercalcemic encephalopathy. Ultimately, our efforts are dedicated to advancing patient care and raising awareness about this relatively uncommon yet clinically significant condition.

5. Conclusions

In conclusion, our clinical profiling of hypercalcemic encephalopathy has illuminated the intricate and diverse nature of this condition. Our comprehensive examination of patients at our tertiary care center has provided valuable insights into the various causes, clinical signs, and short-term outcomes associated with this condition. As we continue to refine our understanding of hypercalcemic encephalopathy, further research is warranted to explore the long-term outcomes, optimal treatment strategies, and potential preventive measures. By building upon this foundational knowledge, we aim to improve patient outcomes, enhance diagnostic accuracy, and contribute to the growing body of evidence in the field of hypercalcemic encephalopathy. Ultimately, our efforts are geared towards advancing patient care and raising awareness about this relatively uncommon yet clinically significant condition.

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