REVIEW

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Hypercalcemic Crisis: A Clinical Review

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ABSTRACT

Hypercalcemia is a common metabolic perturbation. However, hypercalcemic crisis is an unusual endocrine emergency, with little clinical scientific data to support therapeutic strategy. We review the relevant scientific English literature on the topic and review current management strategies after conducting a PubMed, MEDLINE, and Google Scholar search for articles published between 1930 and June 2014 using specific keywords: "hypercalcemic crisis," "hyperparathyroid crisis," "parathyroid storm," "severe primary hyperparathyroidism," "acute hyperparathyroidism," and "severe hypercalcemia" for articles pertaining to the diagnosis, epidemiology, clinical presentation, and treatment strategies. Despite extensive clinical experience, large and well-designed clinical studies to direct appropriate clinical care are lacking. Nonetheless, morbidity and mortality rates have substantially decreased since early series reported almost universal fatality. Improved outcomes can be attributed to modern diagnostic capabilities, leading to earlier diagnosis, along with the recognition that primary hyperparathyroidism is the most common etiology for hypercalcemic crisis. Hypercalcemic crisis is an unusual endocrine emergency that portends excellent outcomes if rapid diagnosis, medical treatment, and definitive surgical treatment are expedited.

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Hypercalcemic crisis is an unusual complication of hypercalcemia that is encountered with decreasing frequency in modern clinical practice. The most common presentation involves a patient with long-standing mild, asymptomatic hypercalcemia resulting from benign primary hyperparathyroidism, presenting with acute decompensation and "new" marked hypercalcemia. Fortunately, timely recognition, diagnosis, and intervention result in excellent outcomes.[1]

DEFINITIONS AND EPIDEMIOLOGY

Hypercalcemic crisis has no uniform standard definition, which makes direct comparison among different studies in the literature difficult. However, a reasonable, yet arbitrary definition may be: an albumin-corrected serum calcium level >14 mg/dL; associated with the presence of multiorgan dysfunction. Typically, organ dysfunction is associated with, or a direct result of, hypercalcemia. The diagnosis should also be considered in severely symptomatic patients despite less marked hypercalcemia.

By 2007 there had been fewer than 350 individual patients with hypercalcemic crisis reported in the literature. However, this is likely to be under-reported, reflecting the heterogeneity of definitions, etiologies, and symptoms attributable to hypercalcemia.[2,3]

Primary hyperparathyroidism is the most common underlying etiology.[1] Parathyroid crisis, parathyroid storm, hyperparathyroid crisis, parathyroid intoxication, parathyroid poisoning, and acute hyperparathyroidism are terms used interchangeably to denote crisis from primary hyperparathyroidism. A large series between 1978 and 2007 reported 252 subjects with crisis attributable to primary hyperparathyroidism.[2] The majority were female (65%), in contrast with other reports indicating a slightly higher incidence in men.[3-7] All age groups are affected, with no specific age predominance. Four percent of women presented during pregnancy.[2] Of the 252 subjects in this series,

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192 had surgical pathology reported. A single parathyroid adenoma was present in 88%. Eight percent of adenomas were located ectopically; including the mediastinum, thymus, tracheoesophageal groove, and retrosternal regions. The mortality rate in this series was 7%. Early series mortality rates approached 100% in patients without timely surgical resection.[3]

Primary hyperparathyroidism is the most common cause of hypercalcemia in ambulatory patients and is often incidentally diagnosed on routine laboratory testing. Single, benign parathyroid adenomas constitute 80%-85% of cases. Diffuse parathyroid gland hyperplasia, double adenomas, and parathyroid carcinoma are far less common. Hanes, in 1938, was the first to report a case of hypercalcemic crisis resulting from parathyroid adenoma.[8] **Table 1** lists potential etiologies of hypercalcemia.

Hypercalcemic crisis is a rare entity in modern practice. A surgical series of patients with primary hyperparathyroidism from the 1970s included 882 subjects and reported only 1.6% presenting in crisis. A more recent single-center series of 1310 consecutive hyperparathyroid patients who underwent parathyroidectomy over a 40-year period reported a 6.7% incidence of crisis.[4]

CLINICAL SIGNIFICANCE

- Despite extensive clinical experience and large case series, prospective studies on Hypercalcemia crisis, which could direct evidence-based clinical care, are lacking.
- Hypercalcemic crisis remains an unusual endocrine emergency.
- Primary hyperparathyroidism is the most common underlying etiology.
- Despite early reports of near universal mortality, modern management has substantially improved outcomes.

CLINICAL PRESENTATION

Hypercalcemic crisis usually evolves from preexisting modest hypercalcemia into an acute severe hypercalcemic exacerbation. Many patients with primary hyperparathyroidism are asymptomatic. However, subtle nonspecific symptoms are often present and attributed to other conditions, making the distinction between symptomatic and asymptomatic mild hypercalcemia troublesome.

Hypercalcemia impacts most organ systems. Gastrointestinal concerns are common and include anorexia, dyspepsia, constipation, nausea, vomiting, and abdominal pain. Pancreatitis, which may be severe and necrotizing, is more common in patients with crisis.[2,9,10] However, it may be argued that pancreatitis re-classifies an uncomplicated patient as one with severe disease, implying crisis.[6,11-13] In a large single-center series of over 1300 patients who underwent parathyroidectomy for primary hyperparathyroidism, the incidence of pancreatitis, altered sensorium, and fatigue were more common in crisis subjects than those with more modest hypercalcemia.[4] Renal manifestations include dehydration, polydipsia, oliguria, acute kidney injury, and nephrocalcinosis. Renal colic may be the presenting complaint. Neurological features are more subtle and include minor neuromuscular symptoms and muscle weakness. Cognitive disturbances include confusion, poor concentration, and personality changes that range from irritability to lethargy and coma. Cardiovascular manifestations include a shortened QT interval with increased susceptibility to arrhythmias and accelerated vascular calcification.

DIAGNOSTIC AND PATHOLOGICAL CONSIDERATIONS

Diagnostic evaluation should focus on establishing or refuting a diagnosis of primary hyperparathyroidism. Frankly elevated or inappropriately normal serum levels of intact parathormone in the presence of hypercalcemia are indicative of primary hyperparathyroidism. History and physical examination should direct further laboratory investigation. Serum parathyroid hormone-related peptide may be elevated in a patient with known cancer. However, local cytokines, osteolytic factors, or production of 1,25-dihydroxyvitamin D by malignant tumor may be responsible for inducing hypercalcemia in malignancy.

There are many other well-described etiologies of hypercalcemia (**Table 1**). However, most are less likely to lead to severe hypercalcemia. Clinicians should keep a broad differential diagnosis in mind when deciding on the utility of ordering further investigations in the work-up. For example, the incidence of hypercalcemia in sarcoidosis is approximately 10%, although hypercalciuria occurs 3 times more frequently.[14] Hypercalcemic, ill, or immobilized patients may decompensate into crisis following calcium mobilization from the skeleton into the extra-skeletal circulation. This is of potential concern with active bone turnover such as in growing children or patients with Paget's disease. Mild hypercalcemia may be exacerbated by high-dose vitamin D and medications including thiazide diuretics, lithium, or calcium-containing antacids. The milk-alkali syndrome is an infrequent etiology of significant hypercalcemia, except for a few sporadic cases described in pregnancy.

Mildly elevated or inappropriately normal parathormone in the face of severe hypercalcemia should prompt consideration of an additional underlying process other than isolated primary hyperparathyroidism. Primary hyperparathyroidism complicated by sarcoidosis, thyrotoxicosis, and immobilization may result in decompensated crisis.[15]

Preoperative localization of parathyroid adenomata with imaging techniques such as ultrasonography, computed tomography, magnetic resonance imaging, and nuclear medicine scintigraphy are accepted in modern practice. Once the diagnosis of primary hyperparathyroidism is biochemically established, imaging modalities should complement, not