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Review Article

Primary Hyperparathyroidism and Gastrointestinal manifestations : Less known entity

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Abstract

Primary hyperparathyroidism (PHPT) is clinically characterised by 'Pentad of PHPT'. PHPT is also associated with various gastrointestinal manifestations viz constipation, acid peptic disease, pancreatitis and cholelithiasis, however all of these are sparsely reported with PHPT. Gastrointestinal manifestations are less specific and literature is silent on cause and effect relationship. Recently, we have shown that constipation (38%) is the most common GI manifestation followed by acid peptic disease (30%), cholelithiasis (28%), pancreatitis (22%) and from PHPT registry of our department (n=300). PHPT pancreatitis often remains undiagnosed for long period due to lack of awareness and low index of suspicion. Pancreatitis in PHPT is multifactorial and curative parathyroidectomy prevents recurrence of pancreatitis. The aim of present review is to increase awareness amongst clinicians and gastroenterologists about gastrointestinal manifestations of PHPT.

Keywords: Primary hyperparathyroidism (PHPT), Gastro-intestinal manifestations, gall stone disease, pancreatitis, peptic ulcer disease

Introduction

Primary hyperparathyroidism (PHPT) results due to unregulated elevated production of parathyroid hormone (PTH) leading to hypercalcemia (Bilezikian and Silverberg, 2004). It is the commonest cause of hypercalcemia in the outpatient setting and is caused by single parathyroid adenoma in 85% of cases (Fraker et al., 2009). The most common presentation is asymptomatic hypercalcemia detected on routine bio-chemical testing. This might explain the asymptomatic presentation of PHPT from the western countries due to universal use of autoanalyzer (Silverberg and Bilezikian, 2006).

However, the presentation of PHPT is still symptomatic in India (Bhansali et al., 2005, Gopal et al., 2010, Muthukrishnan et al., 2008, Pradeep et al., 2011, Shah et al., 2012). The symptoms are usually due to resultant hypercalcemia with multisystem involvement. The cause and effect relationship of PHPT and gastro-intestinal (GI) manifestations is not yet clearly established and most of the studies are old. Here we present a review from the literature world over for GI manifestations associated with PHPT.

Prevalence

There are wide geographical variations, the condition being more prevalent in the west due to routine calcium screening by automatic analyzer (Silverberg, 2000). It is more common in postmenopausal women.

Pathophysiology

Primary hyperparathyroidism is mostly because of solitary parathyroid adenoma and here normal feedback on PTH production by extracellular calcium is lost, whereas in PHPT due to parathyroid hyperplasia, increase in cell numbers increase PTH secretion. The excessive PTH and the hypercalcemia usually leads to the symptoms.

Clinical Features

PHPT is classified as asymptomatic and symptomatic, according to a NIH consensus panel (Bilezikian et al., 2002) approximately three fourths of patients are asymptomatic in the Western world. The classical clinical syndrome of PHPT includes skeletal, renal, cardiovascular, neuromuscular, psychiatric and gastrointestinal, easily remembered as bones, stones, abdominal pains and psychic moans and fatigue overtones. The symptoms are due to prolonged PTH excess leads to bone disease and renal stones or due to hypercalcemia.

GI Manifestations of PHPT

Non-specific Symptoms

The GI manifestations are due to hypercalcemia. GI manifestations as presenting feature of PHPT were described in 1957. Various authors have described GI symptoms as bloating, constipation, nausea, vomiting, anorexia, pain abdomen in symptomatic. But a definite cause and effect relationship has not yet been established. Association of cholelithiasis (Bhadada et al., 2011, Broulik et al., 2005, Christensson and Einarsson, 1977) and pancreatitis (Jacob et al., 2006, Khoo et al., 2009) with PHPT has also been reported. In a recent study, Shah et al. (Shah et al., 2014) described gastrointestinal manifestations in 153 symptomatic histologically

proven patients of PHPT and analyzed their association with biochemical parameters and parathyroid surgery. They reported at least one GI sign or symptom in eighty percent of PHPT patients. The frequency of GI symptoms were found to be abdominal pain (43%), constipation (36%), nausea-vomiting (30%), anorexia (26%) and dyspepsia (24%) (Shah et al., 2014). Symptoms disappeared in abdominal pain in PHPT muscle atony due to reduced neuromuscular excitability by high calcium levels in PHPT could be dyspepsia, gall stones, renal stones etc. Dyspepsia, nausea and vomiting may be explained by increased calcium ion concentration in the majority of the patients in three months post parathyroidectomy. Calcium sensor receptors present along the entire GI tract regulate acid secretion in the stomach (Hebert et al., 2004). Constipation is explained by smooth muscle atony.

Peptic ulcer disease

The association of peptic ulcer disease with PHPT has been reported by various older studies (Barreras and Donaldson, 1967, Frame and Haubrich, 1960, Ostrow et al., 1960) but a prospective study by Carleto et al. has not substantiated this (Corleto et al., 1999). Also the incidence of peptic ulcer disease has markedly reduced after advent of PPIs. All the studies on PHPT & peptic ulcer disease are more than 2 decades old. In a recent prospective study, the presence of ulcers or ulcer symptoms improved in 20% of patients in Zollinger-Ellison syndrome after parathyroidectomy, suggesting an association (Norton et al., 2008).

Cholelithiasis

Few studies (Bhadada et al., 2011, Broulik et al., 2005, Christensson and Einarsson, 1977) have shown the association of gall stone disease and PHPT, the plausible mechanism is thought to be elevated levels of PTH leading to atony of gall bladder (Mok et al., 1989) and hypercalcemia in animal studies have been shown to be favouring lithiatic milieu (Ahrendt et al., 1995). In a recent retrospective study of 120 cases of PHPT, the index authors found a high prevalence of

cholelithiasis as compared to the general population in North India(25.8% vs. 3.1%) , even though no correlation was found between gall stones & serum calcium levels. Exclusion of secondary and tertiary causes of hyperparathyroidism and diagnosis by ultrasound were the strengths of this study (Bhadada et al., 2011).

Pancreatitis

Even though PHPT as a cause of pancreatitis was described as early as 1957(Cope et al., 1957),the exact relation remained questionable and finally ACG guidelines published in 2006 accepted PHPT as an etiology for pancreatitis(Banks and Freeman, 2006).Incidence of pancreatitis in PHPT has varied from 1%-12%(Bess et al., 1980, Bhadada et al., 2008, Carnaille et al., 1998, Curto et al., 2009, Felderbauer et al., 2008, Shepherd, 1996).However, a large US based recent study did not show increase in incidence of pancreatitis in patients with PHPT (Khoo et al., 2009). Acute pancreatitis may, in fact, be the presenting feature of PHPT.The causes of pain in pancreatitis include inflammation, duct obstruction, compartment syndrome, fibrotic encasement of sensory nerves PHPT.Increased PTH levels with elevated calcium levels may increase pancreatic inflammation. Plausible mechanisms for pancreatitis in patients with PHPT include calcium-phosphate deposition in the pancreatic ducts(Ward et al., 1995); calcium-dependent conversion of trypsinogen to trypsin(Frick et al., 1997, Mithofer et al., 1995); increased permeability of pancreatic duct and direct toxic effect of PTH on the pancreas(Bhadada et al., 2008, Jacob et al., 2006).Pancreatitis may improve in after parathyroidectomy. Pancreatitis may follow parathyroid surgery because of an acute rise in calcium levels with manipulation of the parathyroid glands or to a blunted response of calcitonin-producing cells from fatigue.

In contrast to reported association of PHPT with acute pancreatitis , there is not much data on chronic pancreatitis (Ebert, 2010)with PHPT.The index authors compared clinical profile of chronic pancreatitis (CP) secondary to PHPT with that of alcoholic and idiopathic chronic pancreatitis at a

tertiary centre in North India in a retrospective study(Bhadada et al., 2008). They reported different clinical features and bio-chemical markers in CP-PHPT even though the complications were the same in all three types of CP. Corrected calcium, iPTH levels were high and low phosphate levels in CP-PHPT group as compared to alcoholic and idiopathic group. Clinical parameters differentiating CP-PHPT from other types of CP were renal colic ,nephrocalcinosis, nephrolithiasis, bone disease, psychiatric manifestations and neck nodules. Half the patients of CP- PHPT had pancreatic calcification. Parathyroidectomy relieved pain in most of the patients. However, further studies are required to assess the exocrine, endocrine and structural changes of pancreas after parathyroidectomy.

In a recent study, carried out by the index group in 153 patients of symptomatic PHPT patients , effect of gender, biochemical parameters& parathyroidectomy on GI manifestations was analyzed. All 153 patients were histopathologically proven PHPT & 30% (n=46) were men with a mean age 39.2 ± 13.9 yr. Nearly 80% had at least one symptom/sign related to GI system.Nearly one fourth of patients had either gall stone disease or gall bladder removed and higher prevalence in women($p < 0.05$) . Pancreatitis was seen in 27 (18%) of patients with a higher prevalence in men ($p < 0.05$).Serum calcium, phosphate and PTH levels were not associated with high risk of gall stone disease , however, risk of developing pancreatitis was 1.3 times higher with raised serum calcium ($p < 0.05$) (Shah et al., 2014). GI manifestations resolved within 3 months of parathyroidectomy. Only 2/27 patients had recurrence of pancreatitis & was possibly due to severe pancreatic calcification involving the duct also. The biochemical profile was not much different in those with or without GI symptoms.

Conclusion

In conclusion, a high index of suspicion should be kept in mind while evaluating any non-specific abdominal symptoms. The recent studies have reported high GI symptoms presumably caused by

smooth muscle atony. PHPT has been shown to be a risk factor for cholelithiasis, pancreatitis although association with peptic ulcer disease is not clear in the recent literature. These symptoms have been reported to resolve after curative surgical treatment. Further studies are, however, needed to definitely establish the biochemical co-relation between PHPT and GI manifestations.

Footnotes

Authors' Contribution: Dr Aggarwal was responsible for preparation and review of the manuscript. Dr. Bhadada contributed in the design, preparation, and review of the manuscript.

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