SHORT REPORT

Coeliac disease and primary hyperparathyroidism: an association?

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Primary hyperparathyroidism may present with non-specific symptoms, and this may be one reason why patients with coeliac disease fail to improve despite compliance with a gluten-free diet. Seven case reports of primary hyperparathyroidism due to sporadic adenoma occurring in a series of 310 patients with coeliac disease are presented, highlighting the importance of looking for this condition in this population group. A prevalence of primary hyperparathyroidism of 2.3% in this series suggests a significant association between hyperparathyroidism and coeliac disease; most studies have indicated a prevalence of 3 in 1000 in the general population, although one study found that it may be as high as 21 in 1000 in women aged 55–75 years. The average age of patients in our series was 59 years and all but one were women. Further studies are needed to establish a possible association between primary hyperparathyroidism and coeliac disease.

Recent epidemiological studies have shown that coeliac disease is more common than previously thought, with a prevalence approaching 1% in western Europe and the US.¹ The main modes of presentation of adults with coeliac disease may be classified as classic (diarrhoea predominant in a malnourished patient with a malabsorption syndrome) and silent.² The silent group includes those with subtle, atypical presentations and those presenting with complications of coeliac disease, as well as truly asymptomatic people picked up through screening high-risk groups. Most cases remain undiagnosed and potentially are exposed to the risk of long-term complications, which may include the development of malignancy,³ particularly “enteropathy-associated T cell lymphoma”.⁴

In addition, patients with coeliac disease have an increased rate of autoimmune disorder, including type 1 diabetes, thyroid diseases, autoimmune liver disease, autoimmune Addison’s disease and neurological problems. Similar to the development of coeliac disease-associated cancer, the duration of gluten exposure has been reported to be linked to the prevalence of autoimmune disorders in one study,⁵ although this is refuted by others.⁶ In many of these disorders there is a crossover of symptoms with coeliac disease, which may compound the clinical scenario, thereby delaying the diagnosis.

Primary hyperparathyroidism may also present with non-specific features, many of which are shared with coeliac disease, including fatigue, poor appetite and depression.

Primary hyperparathyroidism is caused by the overproduction of parathyroid hormone (PTH), in excess of physiological need. In 75–80% of cases of primary hyperparathyroidism, one or more adenomas account for the overproduction, whereas approximately 20% of cases are secondary to diffuse hyperplasia of all glands. Carcinoma accounts for <2% of all cases.⁷

To date, there has been one report of a possible association between primary hyperparathyroidism and coeliac disease in a patient with confirmed Graves’ disease, who underwent a near-total thyroidectomy, with an incidental finding of a parathyroid adenoma. The authors emphasised the need to look for intestinal malabsorption in the case of normocalcaemic hyperparathyroidism.⁸

We report on 7 patients of a total of 310 followed up in a coeliac disease clinic at Llandough Hospital in South Wales over the course of 8 years, who were found to have primary hyperparathyroidism secondary to a parathyroid adenoma.

CASE REPORTS

Patient A

A 72-year-old woman was diagnosed with coeliac disease in December 2001 and was started on a gluten-free diet (GFD). At the time of her diagnosis, laboratory tests indicated a vitamin D level of 9.1 (8.0–50.0) ng/ml; a calcium level of 2.28 (2.20–2.60) mmol/l; and a PTH level of 21.6 (0.9–5.4) pmol/l. She was started on Calcichew D3 forte and Fosamax for severe osteoporosis in November 2002. She attended a clinic review in May 2003 and was noted as having an increased calcium level at 2.80 mmol/l with an unsuppressed PTH of 5.8 pmol/l and a vitamin D level of 25.8 ng/ml. Her Calcichew was stopped, and she was referred to an endocrine surgeon with a provisional diagnosis of primary hyperparathyroidism. She had parathyroid adenoma localisation studies carried out and excision of the left inferior parathyroid gland. Histological examination disclosed a left inferior parathyroid adenoma weighing 230 mg. Subsequently, her overall sense of well-being improved and repeat laboratory studies in November 2005 showed a calcium level of 2.34 mmol/l and a PTH level of 2.8 pmol/l.

Patient B

A 48-year-old woman was diagnosed as having coeliac disease in February 2002 and was started on a GFD. Laboratory tests at the time of diagnosis showed a vitamin D level of 6.0 (8–50) ng/ml; a calcium level of 2.66 (2.20–2.60) mmol/l; and a PTH level of 9.7 (0.9–5.4) pmol/l. In August 2002, she was prescribed Calcichew D3 forte for severe osteoporosis on a dual energy x ray absorptiometry scan. In December 2002, repeat laboratory tests showed a vitamin D level of 27.6 (8–50) ng/ml; a calcium level of 2.64 (2.20–2.60) mmol/l; and a PTH level of 13.3 (0.9–5.4) pmol/l. Her Calcichew was discontinued, and she was referred to an endocrine surgeon who carried out a partial left superior parathyroidectomy in April 2004. Histological examination confirmed a left superior parathyroid adenoma. She was seen at a follow-up surgical clinic in August 2004 and reported an

Abbreviations: CaR, calcium-sensing receptor; GFD, gluten-free diet; PTH, parathyroid hormone.

Table 1 Association of coeliac disease and primary hyperparathyroidism—patient data

Patient	Date of diagnosis of CD	At diagnosis of primary hyperparathyroidism			Surgical/histological findings	Post-op values		
		Vit D (8–50 ng/ml)	Ca ²⁺ (2.2–2.6 mmol/l)	PTH (0.9–5.4 pmol/l)		Vit D (8–50 ng/ml)	Ca ²⁺ (2.2–2.6 mmol/l)	PTH (0.9–5.4 pmol/l)
C (47 years)	February 2002	33	2.7	5.7	R inferior parathyroid adenoma	59.6	2.37	5.3
D (80 years)	May 1995	—	2.85	18.4	L inferior parathyroid adenoma	14.8	2.26	15.7
E (70 years)	December 2000	20.9	2.81	7.2	R superior parathyroid adenoma	31.7	2.36	2.6
F (87 years)	June 2004	16.7	2.65	11.7	R superior parathyroid adenoma	—	2.35	5.9
G* (59 years)	October 2005	17.9	2.70	14.6	L superior parathyroid adenoma	—	—	—

Ca²⁺, calcium; CD, coeliac disease; L, left; op, operation; PTH, parathyroid hormone; R, right; Vit, vitamin.

—No values were available for these tests from the patient notes.

*No postoperation values were available for this patient.

“injection of new energy” since her operation. Her calcium level at this time was 2.28 mmol/l and the PTH level was 6.6 pmol/l.

Table 1 summarises the details of the remaining five patients.

DISCUSSION

The finding of 7 (2.3%) cases of hyperparathyroidism due to a parathyroid adenoma out of 310 patients with coeliac disease is the largest such series to date; we have since identified one further case of a patient with a suspected parathyroid adenoma, making up a total of eight cases. This is substantially higher than the 2–3 in 1000 prevalence in the general population quoted in most studies,⁹ although similar to the 21 in 1000 prevalence found in 55–75-year-old women in a recent study of prevalence of primary hyperparathyroidism in Europe.¹⁰ The mean age of patients in our series was 59 years and all but one were female. The prevalence of primary hyperparathyroidism in South Wales, however, is not known, and may be substantially different.

The association of primary hyperparathyroidism with coeliac disease has both diagnostic and therapeutic implications. There was a time lag of 1–5 years between diagnoses, invariably because the initial laboratory values indicated low or low-normal vitamin D and calcium levels with what was taken to be compensatory secondary hyperparathyroidism. In addition, coeliac disease and primary hyperparathyroidism share a subtle mode of presentation, with many overlapping, non-specific symptoms that may compound the clinical diagnosis. At least three patients reported improved well-being after resolution of hyperparathyroidism and hypercalcaemia on removal of their parathyroid adenoma, emphasising the need to look for hyperparathyroidism in patients with persistent symptoms despite adherence to GFD.

Tertiary hyperparathyroidism may arise in patients with longstanding undiagnosed coeliac disease after treatment, and is characterised by the autonomous hypersecretion of PTH causing hypercalcaemia. Hyperplasia of the parathyroid glands is the predominant morphological feature and the development of adenoma in tertiary hyperparathyroidism seems to be a rare occurrence, accounting for 5% of cases.¹¹ None of the patients in our series had hyperplasia, which implies that the adenoma arose sporadically rather than as a result of chronic stimulation.

Possibly, primary hyperparathyroidism in these patients is unrelated to their coeliac disease and is a chance finding during routine follow-up. However, detecting a reduced

expression of calcium-sensing receptor protein could also help to confirm the sporadic occurrence of adenoma in association with coeliac disease. The calcium-sensing receptor (CaR) is a transmembrane protein which detects lowered extracellular calcium and is one of the mechanisms controlling PTH release from parathyroid tissue. A markedly decreased level of CaR expression was found in hypertrophied parathyroid glands removed from patients with chronic secondary hyperparathyroidism,¹² as in sporadic parathyroid adenoma, whereas normal adenoma-associated parathyroids taken from patients with sporadic adenoma do not show down regulation in the expression of CaR.¹³ An absence of down regulation in the expression of CaR in normal adenoma-associated tissue in our series of patients lends further weight to the argument for the sporadic occurrence of adenoma, rather than as a result of chronic stimulation of the gland in secondary hyperparathyroidism.

The increased prevalence of coeliac disease in the context of autoimmune conditions such as autoimmune thyroid disease (5.4%) and insulin-dependent diabetes mellitus (5.0%) has received much attention.¹⁴ By prospectively screening patients with confirmed Addison's disease, an association of 12.2% was found with coeliac disease.¹⁵ Carrying out a similar screen for coeliac disease in patients with confirmed primary hyperparathyroidism due to adenomas and an appropriately matched control group may strengthen the evidence for an association. Further studies will be required to establish the link.

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