Case Report

Association of coeliac disease and thyroid disorders

Robert Sciberras

A case study is presented. This involves a woman who presented with features of hyperthyroidism, which were refractory to conventional therapy. She was eventually diagnosed to have co-existing coeliac disease and eventually improved on a diet excluding gluten. A discussion exploring the association between gluten-enetropathy and thyroid dysfunction follows.

Case presentation

AC, a fifty-year old, previously healthy premenopausal woman presented with a six week history of abdominal discomfort, and diarrhoea (up to ten times during the day and three times during the night). There was also significant weight loss: 10 kilograms over the same period. The stools were brown coloured and the patient denied rectal bleeding or melaena. The appetite was unaffected. The patient also felt very weak and depressed. Her appearance was that of a physically weak lady. She had exophtalmos of both eyes more marked on the right, mildly prominent thyroid gland, and tremor of the outstretched hands. Her pulse was 120 beats per minute, regular and of good volume. The rest of the examination was unremarkable. A diagnosis of thyrotoxicosis was made and the patient was started on carbimazole 10mg three times a day and propranolol 20mg three times a day. Thyroid function tests were taken and the results confirmed a hyperthyroid state: Thyroid Stimulating Hormone (TSH) was <0.004 uIU/ml (*reference range 2.76-6.45*), free thyroxine (FT4) was 64.6 pmol/l (*reference range 10.3-24.45)* and free tri-iodothyronine (FT3) was at a level of 17.7 pmol/l (*reference range 2.76-6.45)*. A full blood count revealed a haemoglobin of 11.2 g/dL which is just below the reference range. The Mean Corpuscular Volume (MCV) was 81.5 fL which was also slightly below the normal range. Antithyroid antibodies (ATA) were 212 IU/mL (*reference range <35)*.

A week later, the patient came for a follow-up visit. Unfortunately in spite of being compliant with treatment her clinical condition had not changed. She was still feeling very weak and all her symptoms were still present. In particular she had lost another two kilograms of weight. A malabsorption pathology leading to poor absorption of carbimazole was suspected and further investigations were undertaken. Screening serological tests for coeliac disease were positive: anti-tissue transglutaminase (TG) IgG was 2.7U/ml (within reference range) but anti-tissue TG IgA was >100 U/ml (*values above 10 are positive)* and anti-endomysial IgA (AEA) was reported as positive ++. Gastroscopy and duodenal biopsies showed increased number of intraepithelial lymphocytes, severe mixed inflammatory infiltration of the lamina propria with plasma cell predominance, marked villous atrophy and crypt hyperplasia. This microscopic picture was consistent with a diagnosis of coeliac disease, Marsh's Type 3b.

The patient embarked on a gluten free diet and her symptoms started to improve, presumably due to better absorption of anti-thyroid medication. An ultrasound of the thyroid revealed a nodule in which nuclear imaging showed increased tracer uptake. The patient eventually underwent radio–iodine thyroid ablation after a 4 month period on carbimazole, progressed to hypothyroidism and is on replacement thyroid therapy, together with a gluten free diet. She is now totally asymptomatic, has regained her lost weight and feels well.

Discussion

Coeliac disease (CD), also called gluten-induced enteropathy, can present in various ways. Patients can present with symptoms, signs or even abnormal blood investigations taken as routine or for other complaints. There is a high prevalence of undiagnosed CD in the general population largely as a result of the many atypical manifestations of the disease. The most common clinical presentation of CD would be persistent non-specific gastrointestinal upset and constitutional symptoms. These clinical features are also found in thyroid dysfunction, especially thyrotoxicosis. The case history presented above involved a lady who presented with full blown features of thyrotoxicosis which proved refractory to anti-thyroid medication, possible due to malabsorption. CD was diagnosed eventually and the

Key words

Hyperthyroidism, coeliac disease, gluten, gluten-enteropathy

Robert Sciberras MD, FRCP (Lond)
Department of Medicine, Gozo General Hospital, Gozo
Email: robscib@maltanet.net

patient finally improved only when her diet excluded gluten-containing food.

CD is relatively common in Western populations with a prevalence of around 1%.[1] However increased prevalence of CD has been found in patients with autoimmune thyroid diseases, Type 1 diabetes mellitus, autoimmune liver diseases and inflammatory bowel disease. Conversely there is also increased prevalence of immune based disorders among patients with CD. In particular the prevalence of CD in autoimmune thyroid disorders was found to be between 2% and 5%[1] or approximately 4-15 times higher than the general population.[2] This is not altogether surprising given that these conditions share similar HLA haplotypes (HLA class II , DqB1*0502 genotype)and are associated with the gene encoding cytotoxic T-lymphocyte-associated antigen-4.[1,3] Other immunogenetic theories include: antigenic mimicry, damage-induced neoantigen exposure, altered intestinal permeability, idiotype network deregulation (modification of the immune response by anti-idiotypic antibodies) and epitope spreading (development of an immune response to epitopes distinct from, and non-cross reactive with, the disease-causing epitope).[4] Spadaccino *et al*. demonstrated an increased prevalence of CD in adult European and Italian patients with auto-immune thyroid disease.[5] An IgA deficiency is the most frequent immunodeficiency in humans and in general high frequency of this disorder was demonstrated in those with auto-immune diseases. In a Dutch study, Hadithi *et al* confirmed the association between Hashimoto's thyroiditis and CD.[6] Valentino *et al.* suggested a significant high prevalence (3.3%) of CD in patients with autoimmune thyroid disease particularly Hashimoto's thyroiditis.[7] Mankai *et al*. found an association between CD and Graves' disease in a study carried out in Tunisia. Caputo *et al.*reported a case similar to this case report where gluten-induced enteropathy was revealed by resistance to levothyroxine treatment in a lady with surgically-induced hypothyroidism.[8,9] Another patient had a history of thyroid enlargement with normal thyroid function and positive anti-peroxidase antibodies. She presented with hypocalcaemia after total thyroidectomy and was eventually diagnosed to suffer from CD.[10] Another patient with idiopathic autoimmune hypoparathyroidism who developed hyperthyroidism due to Graves disease was subsequently diagnosed with CD. The give-away clue was malabsorption of L-thyroxine.[11] Malabsoption to L-thyroxine can be partial and can result in the patient needing high doses of L-thyroxine. Silva *et al* suggested that compensation of hypothyroidism requiring doses of L-thyroxine in the region of 325µg/day should lead the clinician to actively exclude co-existing CD.[12] A study from Toulouse suggests screening for CD if hypothyroid patients require a daily dose above 2 micrograms per kg body weight, whatever their age.[13] Cubiella *et al*. describe a case which is practically identical to the one reported above: the patient was a 65-year old woman who presented with CD and autoimmune hyperthyroidism simultaneously.[14] An interesting study from Turin, Italy found that thyroid disease was 3-fold higher in coeliac patients than controls.[15] In distinct cases, gluten withdrawal reversed the thyroid abnormality.

CD has been associated with T-cell lymphoma of the intestine as well as hepatosplenic lymphoma, a specialised peripheral type of T cell lymphoma. Freeman reported a case where CD was associated with T-cell lymphoma of the thyroid.[16] A study from New York identified an increased risk of papillary carcinoma of the thyroid, in patients with CD; the patients were following a proper gluten-free diet.[17]

Finally a link has been found between CD, panic disorders and major depressive disorder. It has been postulated that association with subclinical thyroid disease appears to represent a significant risk factor for these psychiatric disorders.[18]

Several authors are now urging screening for CD in patients with thyroid disorders and vice versa. [19-26] Screening for CD should include testing for anti-tissue transglutaminase IgG and IgA, which is a blood test readily available in Malta. Should this be positive (>10.0 units/ml) or weakly positive (6.0-10.0 units/mL), a duodenal biopsy via gastroscopy should be taken. The histopathologist will then confirm or otherwise the diagnosis of CD since duodenal biopsy is the gold standard for definite diagnosis. In IgA–deficient patients clinical suspicion may warrant a duodenal biopsy in spite of negative serological tests since false negative results can occur.

Conclusion

There is an association between thyroid disorders and CD. When a patient presents with either condition, one should keep in mind the possibility of the co-existence of the other. This is true especially if thyroid signs and symptoms do not improve with what seems to be adequate treatment or if the patient requires much higher doses than usual. The lesson to be learnt from this case study above is that several diseases frequently co-exist with CD and that patients should be screened for several other conditions.

References

1. Ch'ng CL, Jones MK, Kingham JG. Celiac disease and autoimmune thyroid disease. Clin Med Res 2007;5:184-92.
2. Fanciulli G, Tomasi PA, Caucci F, Lai E, Sanciu F, Delitala G. Screening for celiac disease in patients with autoimmune thyroid disease: from research studies to daily clinical practice. Ann Ital Med Int. 2005;20:39-44.
3. Velluzzi F, Caradonna A, Boy MF, Pinna MA, Cabula R, Lai MA, *et al.* Thyroid and coeliac disease: clinical, serological and echocardiographic study. Am J Gastroenterol. 1998;93:976-9.
4. Shaoul R, Lerner A. Associated autoantibodies in celiac disease. Autoimmun Rev. 2007;6: 559-65.
5. Spadaccino AC, Basso D, Chiarelli S, Albergoni MP, D'Odorico A, Plebani M, *et al.* Celiac disease in North Italian patients with autoimmune thyroid diseases. Autoimmunity. 2008; 41:116-21.
6. Hadithi M, de Boer H, Meijer JW, Willekens F, Kerckhaert JA, Heijmans R *et al.* Coeliac disease in Dutch patients with Hashimoto's thyroiditis and vice versa. World J Gastroenterol. 2007;13:1715-22.
7. Valentino R, Savastano S, Tommaselli AP, Dorato M, Scarpitta MT, Gigante M, *et al.* Prevalence of coeliac disease in patients with thyroid autoimmunity. Horm Res. 1999; 51:124-7.

8. Mankai A, Chadli-Chaieb M, Saad F, Ghedira-Besbes L, Ouertani M, Sfar H, *et al*. Screening for celiac disease in Tunisian patients with Graves' disease using anti-endomysium and anti-tissue transglutaminase antibodies. Gastroenterol Clin Biol. 2006;30:961-4.
9. Caputo M, Brizzolara R, Schiavo M, Salmaso C, Pesce G, Bagnasco M. Occurrence of overt celiac disease in the elderly following total thyroidectomy. J Endocrinol Invest. 2006;29:831-3.
10. Harzallah F, Daoud I, Bouzid C, Oueslati A, Kanoun F, Silmane H. Celiac disease revealed by hypocalcemia complicating total thyroidectomy: a case report. Ann Endocrinol (Paris). 2006;67:357-9..
11. Khandwala HM, Chibbar R, Bedi A. Celiac disease occurring in a patient with hypoparathyroidism and autoimmune thyroid disease. South Med J. 2006;99:290-2.
12. Silva CM, Souza MV. Autoimmune hypothyroidism nonresponsive to high doses of levothyroxine and severe hypocalcemia. Arq Bras Endocrinol Metabol. 2005;49:599-603.
13. d'Estève-Bonetti L, Bennet AP, Malet D, Hoff N, Louvet JP, Caron P. Gluten-induced enteropathy (coeliac disease) revealed by resistance to treatment with levothyroxine and alfacalcidol in a sixty-eight-year-old patient: a case report. Thyroid. 2002;12:633-6.
14. Cubiella J, Bustamante J, Sans M, Ramirez A, Feu F, Pique' JM. Simultaneous presentation of autoimmune thyroiditis and celiac disease in an adult. Gastroenterol Hepatol. 1998;21:442-4.
15. Sategna-Guidetti C, Volta U, Ciacci C, Usai P, Carlino A, De Franceschi L, *et al*. Prevalence of thyroid disorders in untreated adult celiac disease patients and effect of gluten withdrawal: an Italian muliticenter study. Am J Gastroeneterol. 2001;96:751-7.
16. Freeman HJ. T cell lymphoma of the thyroid gland in celiac disease. Can J Gastroeneterol. 2000;14:635-6.
17. Kent L, McBride R, McConnell R, Neugut AI, Bhagat G, Green PH. Increased risk of papillary thyroid cancer in celiac disease. Dig Dis Sci. 2006;51:1875-7.
18. Carta MG, Hardoy MC, Boi MF, Mariotti S, Carpiniello B, Usai P. Association between panic disorder, major depressive disorder and celiac disease: a possible role of thyroid autoimmunity. J. Pscychosom Res. 2002;53:789-93.
19. Collin P, Salmi J, Hällström O, Reunala T, Pasternack A. Autoimmune thyroid disorders and celiac disease. Eur J Endocrinol. 1994;130:137-40.
20. Cuoco L, Cert M, Jorizzo RA, De Vitis I, Tursi A, Papa A, *et al*. Prevalence and early diagnosis of coeliac disease in autoimmune thyroid dirsorders. Ital J Gastroenterol Hepatol. 1999;31:283-7.
21. Chemli J, Braham N, Boughattas S, Harbi A. Besdow's disease and celiac disease in an adolescent with Down's syndrome. Rev Med Interne. 2006;27:791-3.
22. Iurio R, Mercuri V, Barbarulo F, D'Amico T, Mecca N, Bassotti G, *et al*. Prevalence of celiac disease in patients with autoimmune thyroiditis. Minerva Endocrinol. 2007;32:239-43.
23. Mainardi E, Montanelli A, Dotti M, Nano R, Moscato G. Thyroid-related autoantibodies and celiac disease: a role for a gluten-free diet? J Clin Gastrenterol. 2002;35:245-8.
24. Hakanen M, Luotola K, Salmi J, Laippala P, Kaukinen K, Collin P. Clinical and subclinical autoimmune thyroid disease in adult celiac disease. Dig Dis Sci. 2001;46:2631-5.
25. Larizza D, Calcaterra V, De Giacomo C, De Silvestri A, Asti M, Badulli C, *et al*. Celiac disease in children with autoimmune thyroid disease. J Pediatr. 2001;139:738-40.
26. Volta U, Ravaglia G, Granito A, Forti P, Maioli F, Petrolini N, *et al*. Coeliac disease in patients with autoimmune thyroiditis. Digestion. 2001;64:61-5.

Corinthia Group Prize in Paediatrics, 2008

The Corinthia Group Prize in Paediatrics was awarded to Dr Luise Reichmuth, who obtained the highest aggregate mark over the combined examinations in Paediatrics in the fourth and final year of the undergraduate course. As always, competition for the Corinthia Group Prize was fierce, with six candidates vying for the honour! Whilst offering our congratulations to Dr Reichmuth, we would also like to congratulate all those undergraduates (now doctors) who performed admirably during the undergraduate course in Paediatrics. In the accompanying photograph, Dr Reichmuth is seen receiving a cheque for €233 from Professor Simon Attard Montalto, Head of Paediatrics at the Medical School. Finally, the Academic Department of Paediatrics and Medical School remain indebted and are extremely grateful to the Corinthia Group for their ongoing support.

Professor Simon Attard Montalto