International Journal of Celiac Disease, 2016, Vol. 4, No. 3, 84-86
Available online at http://pubs.sciepub.com/ijcd/4/3/5

DOI:10.12691/ijcd-4-3-5

Autoimmune Adrenal Insufficiency in Celiac Disease

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Abstract Celiac disease is an immune-mediated intestinal disorder that may be associated with other immune-mediated extra-intestinal disorders, including immune-mediated endocrine diseases, such as autoimmune thyroiditis, most often with hypothyroidism. Other monoglandular autoimmune endocrine disorders may also occur, including autoimmune adrenal insufficiency (Addison's disease). In celiac disease, clinical features of adrenal failure may be limited, difficult to differentiate from symptoms that might be attributed to celiac disease, or even life-threatening. In others with celiac disease, a polyglandular autoimmune syndrome has also been reported. Recent screening studies from multiple countries, particularly in Europe, have indicated that patients with autoimmune adrenal failure or Addison's disease should be carefully screened for occult or silent celiac disease. Up to 10% of Addisonian patients may be serologically positive and histopathological features of untreated celiac disease may be detected, even with clinically occult intestinal disease. Celiac disease patients with a monoglandular autoimmune disorder should also be followed carefully for the later appearance of other autoimmune endocrine disorders as these may not all appear at the time of diagnosis of celiac disease, but sporadically during the life-long clinical course of celiac disease.

Keywords: *Addison's Disease, Autoimmune Adrenal Insufficiency, Celiac Disease, Hypothyroidism, Polyglandular Endocrine Failure*

Cite This Article: Hugh J Freeman, "Autoimmune Adrenal Insufficiency in Celiac Disease." *International Journal of Celiac Disease*, vol. 4, no. 3 (2016): 84-86. doi: 10.12691/ijcd-4-3-5.

1. Introduction

Celiac disease is an immune-mediated small intestinal mucosal disorder that responds to restriction of dietary gluten [1]. In recent years, other sites have also been documented to have an immune-mediated inflammatory process associated with altered function. Sometimes, disease in an extra-intestinal site leads to subsequent detection of celiac disease. At other times, the disease in an extra-intestinal site is detected concomitantly or after detection of celiac disease. Different individual endocrine glands, particularly the thyroid gland [2], may be affected. This may occur either as the single or sole endocrine site of extra-intestinal involvement, or at times, as a "poly-glandular" disorder involving multiple different glands, often with diminished function. Here, the specific relationship between celiac disease and adrenal cortical involvement and its clinical relevance are described.

2. Adrenal Cortex

The adrenal cortical glands are paired pyramidal structures situated atop the kidneys that emerge during the 4th to 6th week of fetal development. A few weeks later, the fetal adrenal cortex is invaded by cells from the neural crest to form a separate adrenal medulla. The adrenal cortical cells appear able to both absorb cholesterol from the circulating blood and synthesize cholesterol in adrenal cortical cells. Accumulated cholesterol is then enzymatically converted to several steroid hormones. Of several steroids produced, cortisol and aldosterone are at least 2 of the most critical ones for normal human health. Adrenocorticotropic hormone (ACTH), produced in the anterior pituitary gland, is a key regulator of adrenal cortical function involved in production of plasma cortisol and other steroid hormones by the adrenal cortex. Although located at a separate and distant site from the adrenal cortex, the pituitary gland per se, may also be affected by an immune-mediated inflammatory process (eg., inflammatory bowel disease), and is, interestingly, also embryologically-derived from the fetal gut, specifically, Rathke's pouch [3].

3. Adrenal Insufficiency

Regardless of the precise cause of adrenal gland destruction, the result, especially if both glands are affected, is impaired adrenal function or failure, labeled by the eponym for the syndrome, Addison's disease. Historically, most cases were attributed to infectious causes, particularly tuberculosis, but in more recent years, the cause has not been so readily defined, and often the disorder is labeled either "idiopathic" or due to "autoimmune" disease of both glands. In most, the clinical course in this setting appears to be insidious and slowly progressive so few symptoms may be evident, especially early in the clinical course. Most often, the major clinical features can be attributed to a reduction in circulating cortisol and aldosterone. In females, loss of adrenal androgen production may also be noted. The main symptoms have been detailed elsewhere in standard endocrine texts [4] and some are summarized here.

Interestingly, there may be clinical similarities in presentation with celiac disease in the absence of a specific endocrine disorder making diagnosis of an endocrine disorder complicating celiac disease even more difficult.

4. Clinical Features of Adrenal Cortical Failure

Cortisol deficiency can lead to: anorexia, nausea and vomiting, weight loss, lethargy, confusion, impaired gluconeogenesis, impaired fat mobilization and utilization (i.e, wasting of fat depots), fasting hypoglycemia, hypotension, impaired ability to excrete "free water", enhanced ACTH and melanocyte stimulating hormone (MSH) secretion causing mucocutaneous hyperpigmentation and reduced response to physiological stresses, including trauma, infection, and fasting. *Aldosterone deficiency* can lead to: impaired ability to conserve sodium and excrete potassium with hyponatremia and hyperkalemia, decreased extracellular fluid volume, hypotension, reduced cardiac output and renal blood flow, pre-renal azotemia, postural syncope, and, rarely shock.

In one dramatic case seen by the author, a known 45 year old celiac with associated hypothyroidism developed unexplained and persistent nausea and vomiting. She had an elective endoscopic evaluation arranged. However, she was first recognized (just before the procedure) to have clinical and laboratory features suggestive of concomitant Addison's disease. She was mildly hypotensive and had a "tanned skin" appearance while initial routine laboratory features revealed hyponatremia and hyperkalemia. Subsequent laboratory investigations (including an ACTH stimulation test, rather than endoscopy!) resulted in diagnosis of adrenal insufficiency. Interestingly, a similar female celiac disease patient had been previously recorded in a case report with polyendocrine failure [5] and in 2 patients with Addison's disease and selective IgA deficiency in a 25 year Galway celiac disease registry [6]. Finally, other difficulties in diagnosis were underlined in a male asthmatic celiac child using a moderate dose of inhaled budesonide apparently masking underlying Addison's disease [7].

5. Celiac-associated Adrenal Failure

5.1. Studies in Addison's Disease

A prospective Irish screening study by O'Leary *et al* [8] of Addison's patients revealed that 5 (or 12.2%) had celiac disease based on serological studies and biopsy review. These included 3 previously diagnosed celiac patients and 2 new cases (with positive endomysial antibodies (EMA) and small intestinal biopsies). In a report from Norway [9], Myhre *et al* also noted a high frequency of celiac disease in patients with autoimmune adrenocortical failure. In their report, a total of 76 patients with adrenal failure were evaluated. Of these, 44 were female and 52% had polyendocrine failure; all had serological screening with antibodies against gliadin, EMA and tissue transglutaminase (tTG). In all 5 of the Addison's patients with both positive EMA and elevated levels of tTG, histopathological changes attributed to celiac disease were detected on small intestinal biopsies. One added patient had celiac disease recognized before the research study. All 6 of these patients had the celiac disease associated histocompatibility leukocyte antigen (HLA) haplotype, DR3-DQ2, for an overall total celiac disease prevalence of 7.9% leading the investigators to recommend screening for celiac disease in Addison's patients. In another study from Finland [10], Kaukinen *et al* surveyed their patients with more than one autoimmune endocrinologic disorder for evidence of celiac disease. These included patients with insulin-dependent diabetes mellitus, autoimmune thyroid disease or Addison's disease. A total of 7 had celiac disease (or, 11%), including 6 defined earlier along with 1 new case. Similarly, in an Italian study [11], 17 consecutive patients with Addison's disease (including 14 females, mean age 53.9 years) were evaluated. Of these, 1 (or. 5.9%) was EMA positive with a duodenal biopsy reported to show subtotal villous atrophy. The investigators noted that similarity in symptoms as well as treatment of Addison's disease that might mask underlying celiac disease. In a database study from Sweden [12] using a national register, a statistically significant positive association between reported diagnoses of celiac disease and Addison's disease was described. The risk was increased in both children and adults, but independent of temporal sequence. As a result, the investigators recommended screening of patients with a diagnosis of Addison's disease for celiac disease and suggested increased awareness of potential Addison's disease in the course of celiac disease. In a study [13] of 109 with autoimmune Addison's disease from Italy, 2 with a known diagnosis of celiac disease (or, 1.8%) and 4 with newly detected celiac disease (or, 3.7%) were noted, including 2 with IgA deficiency. In this study, 81 of 109 (or, 74.3%) also had auto-antibodies demonstrated to adrenal cortex using an indirect immunfluoresence method to human adrenal glands and a previously reported immunoprecipitation assay [14]. Similar observations were reported in a study [15] of 85 Polish patients (61 females) with autoimmune Addison's disease. In their evaluation using tissue transglutaminase, 3.5% were seropositive.

5.2. Studies in Autoimmune Polyglandular Syndrome

A number of studies have been reported as the classification and pattern differentiation of this entity including adrenal cortical failure has emerged and developed over time. In one report [16], different age groups were largely considered in classification of 2 major subtypes. APS type 1 (juvenile form) was detected in early adolescence or infancy and was characterized by multiple endocrine deficiencies, mucocutaneous candidiasis, ectodermal dystrophy and several endocrine disorders. The latter usually included Addison's disease, type 1 diabetes mellitus, thyroid disease, hypoparathyroidism and hypogonadism. APS type 2 (adult form) was usually detected later in the 3rd or 4th decade, often with a predominance of females. In this pattern, Addison's disease, type 1 diabetes mellitus and thyroid disease were common, but hypoparathyroidism was rare and mucocutaneous candidiasis was not noted [17]. The endocrine pattern in the polyendocrine glandular syndrome

that appeared most often with celiac disease was the type 2 adult form, even though hypoparathyroidism has been occasionally recorded in celiac disease [18]. Another study [19] reflected this evolution in classification of the polyglandular syndromes. The investigators confirmed that APS type 1 most often occurred in children and also included Addison's disease while APS type 2 was more common in adults and Addison's was usually diagnosed with thyroiditis, labeled with the eponym, Schmidt's syndrome, or type 1 diabetes mellitus, labeled with so-called, Carpenter's syndrome. In the absence of adrenal failure, a type 3 pattern was noted. Finally, a type 4 pattern could occur in celiac disease with autoimmune hypophysitis [19]. The authors also noted that detection of a monoglandular endocrinopathy may only be the first stage in the ongoing and later clinical appearance of other endocrinopathies, implying that close and ongoing active follow-up of celiac disease patients may be critically important in later detection of late-emerging endocrine disorders.

Besides the potential for later development of a newly emergent endocrine disorder in celiac disease, some patients, particularly with occult adrenal failure, if unrecognized, may make treatment of another endocrine disorder more difficult, and even appear refractory to routine treatment, particularly hypothyroidism. Clearly, a number of factors need to be considered if high thyroxine doses are needed to manage concomitant hypothyroidism in a celiac patient. These include poor adherence to either drug (thyroxine) therapy or a strict gluten-free diet, or both. Impaired small intestinal absorption may be result. In addition, serum levels may be altered by Addison's disease in this setting of polyglandular endocrinopathy and diagnosis of occult Addison's disease may be defined with an ACTH stimulation test [20]. Moreover, the added "stress" of thyroxine administration in a patient with unrecognized adrenal failure should be considered in a celiac patient with newly diagnosed hypothyroidism. In this setting, exclusion of Addison's disease prior to thyroxine administration may be important.

6. Conclusion

Celiac disease may be associated with other immune-mediated disorders, including endocrinopathies, such as thyroiditis causing hypothyroidism. In addition, autoimmune Addison's disease may be closely linked to celiac disease as a monoglandular disorder, or ultimately, a polyglandular form of autoimmune endocrine insufficiency. Ongoing follow-up is important as other organ specific involvement may not occur concomitantly with diagnosis of celiac disease or even with detection of an associated apparent monoglandular autoimmune endocrine disorder. In autoimmune adrenal failure, the prevalence of occult celiac disease approaches 10% and so screening has been recommended.

References

[1] Freeman HJ. Celiac Disease. Reference Module in Biomedical Sciences. 2014 Elsevier. 15-Oct-14.

[2] Freeman HJ. Celiac-associated autoimmune thyroid disease: a study of 16 patients with overt hypothyroidism. Can J Gastroenterol 1995; 9: 242-246.

[3] Freeman HJ, Maguire J. Sellar inflammatory mass in inflammatory bowel disease. Can J Gastroenterol 2010; 24: 58-60.

[4] Liddle GW, Melmon KL. The Adrenals. Chapter 5. In: Textbook of Endocrinology 5th Edition, Ed. Williams RH, W B Saunders Company, Philadelphia, London, Toronto, 1974; 233-322.

[5] Valentino R, Savastano S, Tommaselli AP, Dorato M, Scarpitta MT, Gigante M, Lombardi G, Troncone R. Unusual association of thyroiditis, Addison's disease, ovarian failure and celiac disease in a young woman. J Endocrinol Invest 1999; 22: 390-394.

[6] Heneghan MA, McHugh P, Stevens FM, McCarthy CF. Addison's disease and selective IgA deficiency in two celiac patients. Scand J Gastroenterol 1997; 32: 509-511.

[7] Stenhammar LC, Hogberg LM, Nordwall M, Stromberg LG. Moderate dose inhaled budesonide disguising symptoms of Addison's disease in an asthmatic boy with silent celiac disease. J Pediatr Pharmacol Ther 2005; 10: 100-103.

[8] O'Leary C, Walsh CH, Wieneke P, O'Regan P, Buckley B, O'Halloran DJ, Ferriss JB, Quigley EM, Annis P, Shanahan F, Cronin CC. Celiac disease and autoimmune Addison's disease: a clinical pitfall. QJM 2002; 95: 79-82.

[9] Myhre AG, Aarsetoy H, Undlien ED, Hovdenak N, Aksnes L, Husebye ES. High frequency of celiac disease among patients with autoimmune adrenocortical failure. Scand J Gastroenterol 2003; 38: 511-515.

[10] Kaukinen K, Collin P, Mykkanen AH, Partanen J, Maki M, Salmi J. Celiac disease and autoimmune endocrinologic disorders. Dig Dis Sci 1999; 44: 1428-1433.

[11] Biagi F, Campanella J, Soriani A, Vailati A, Corazza GR. Prevalence of celiac disease in Italian patients affected by Addison's disease. Scand J Gastroenterol 2006; 4: 302-305.

[12] Elfstrom P, Montgomery SM, Kampe O, Ekbom A, Ludvigsson JF. Risk of primary adrenal insufficiency in patients with celiac disease. J Clin Endocrinol Metab 2007; 92: 3595-3598.

[13] Betterle C, Lazzarotto F, Spadaccino AC, Basso D, Plebani M, Pedini B, Chiarelli S, Albergoni M. Celiac disease in North Italian patients with autoimmune Addison's disease. Eur J Endocrino 2006; 154: 275-279.

[14] Betterle C, Volpato M, Pedini B, Chen S, Rees-Smith B, Furmaniak J. Adrenal cortex autoantibodies (ACA) and steroid-producing cells autoantibodies (StCA) in patients with Addison's disease: comparison between immunofluorescence and immunoprecipitation assays. J Clin Endo Metab 1999; 84: 618-622.

[15] Fichna M, Fichna P, Gryczynska M, Walkowiak J, Zurawek M, Sowinski J. Screening for associated autoimmune disorders in Polish patients with Addison's disease. Endocrine 2010; 37: 349-360.

[16] Van den Driessche A, Eenkhooorn V, Van Gaal L, De Block C. Type 1 diabetes and autoimmune polyglandular syndrome: a clinical review. J Medicine 2009; 67: 376-387.

[17] Lakhotia M, Pahadia HR, Kumar H, Singh J, Tak S. A case of autoimmune polyglandular syndrome (APS) type II with hypothyroidism, hypoadrenalism, and celiac disease---a rare combination. J Clin Diagn Res 2015; 9: OD01-3.

[18] Matsueda K, Rosenberg IH. Malabsorption with idiopathic hypoparathyroidism responding to treatment with coincident celiac sprue. Dig Dis Sci 1982; 27: 269-273.

[19] Hrubiskova K, Jackuliak P, Vanuga P, Pura M, Payer J. Autoimmune polyendocrine syndrome type 2 associated with autoimmune hypophysitis and celiac disease. Vnitr Lek 2010; 56: 1169-1176.

[20] Ramadhan A, Tamilia M. Treatment-refractory hypothyroidism. CMAJ 2012; 184: 205-209.