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Sjögren's Syndrome Associated with Celiac Disease

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Abstract **Background**: Autoimmune diseases tend to run in families and the affected persons are prone to additional autoimmune conditions. This is the case for celiac disease (CD) and Sjögren's syndrome (SS). **Objectives**: To describe a patient with both diseases and to analyze the clinical, therapeutic and evolutionary characteristics of published patients with SS associated with CD. **Methodology**: A systematic review of articles published in PubMed, MEDLINE, LILACS and Scielo dating from 1966 to May 2020, was conducted, using the following search words: Sjögren's syndrome, Celiac disease. Only English, German and French publications were considered. **Results**: Only 16 studies with 31 patients with SS associated CD were depicted. Adding the present case would mount the total to 17 studies, describing 32 patients. There are 6 observational studies and 10 case reports. In relation to demographics, age varied from 10 to 73 years old, with a median of 45 years and the great majority were female (21/32 patients). SS preceded CD manifestations in 7 studies, CD was the first presentation in 6 articles and simultaneous diseases was observed in 4 reports. Time elapsed between the two diseases varied from 2 to 33 years. Autoantibodies related to SS showed that anti-Ro and anti-La were positive in 8/17, while CD-related antibodies were positive in 12/17 studies. Regarding therapy, the majority received a gluten-free diet as CD therapy (13/17 studies). Glucocorticoid was prescribed in 6/17 studies and hydroxychloroquine in 4/17. When described, all studies demonstrated improvement of CD manifestations and 7/17 improved SS symptoms. **Conclusion:** The present comprehensive review evaluated all published cases of SS and CD of the literature. In the majority, SS precedes CD and all patients had good responses to appropriate therapy. It is hoped that increased awareness of the combination of SS and CD will result in earlier diagnosis and therapy and improved outcome.

Keywords: *Sjögren's syndrome, celiac disease, dermatitis herpetiformis, autoantibodies, poly-autoimmunity, multiple autoimmune syndrome*

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1. Introduction

Sjögren's syndrome (SS) is an autoimmune condition characterized by sicca syndrome that affects the body's moisture-producing glands. It manifests by dry eyes, mouth, skin, vagina, a chronic cough, numbness in the arms and legs, feeling tired and muscle and joint pains [1]. It is a multi-organ and multi-system condition with a prevalence of 2-10 per 10,000 people in the United States [2]. Diverse autoimmune manifestations or associations were described in SS, rheumatoid arthritis, primary biliary cirrhosis, Hashimoto thyroiditis and rarely Celiac disease (CD) or dermatitis herpetiformis [3,4,5].

Celiac disease is an autoimmune condition presented in genetically predisposed individuals upon intake of gluten-containing prolamins (i.e. wheat, barley, rye and oat) or their ingredients. Its prevalence Is much higher than SS, affecting around 1-1.5% of Western populations [6,7,8]. Geo-epidemiological, HLA-DQ2/8 genotypes frequency, co-localization of increased gluten consumption accompanied by CD incidence surge, reinforce the environmental-genetic interplay in CD evolvement [9]. It is known that frequently it is misdiagnosed, the ratio of diagnosed/undiagnosed individuals can mount to 1/7, respectively [10]. The phenotype is changing: incidence is increasing, age of presentation is increasing while less gastrointestinal symptoms are replaced by extraintestinal manifestations [11]. The mosaic of autoimmunity pertains to poly-autoimmunity. Patients with a single autoimmune disorder are at 25% risk of development additional autoimmune conditions [12,13]. The possibility of three or more autoimmune disorders occurring in the same patient cannot be fortuitous and suggests a pathogenic link between each of them. The present study aims therefore to describe the clinical, therapeutic and evolutionary

characteristics of patients with SS who had concomitant CD and dermatitis herpetiformis and review the literature on CD and SS associations.

2. Material and Methods

Patient Selection: The present research is characterized as a descriptive and transversal study with a retrospective analysis of the medical records of a patient diagnosed with both SS, CD and dermatitis herpetiformis. A literature review of SS and CD association is added. An informed consent was signed by the patient.

Literature Review: A systematic research of articles published in PubMed, MEDLINE, LILACS and Scielo dating from 1966 to May 2020, was performed. All the researched articles are based on “Sjögren's syndrome” and “Celiac/Coeliac disease” in the following languages: English, German and French. Furthermore, a detailed case report on a patient presented with CD and dermatitis herpetiformis, subsequently diagnosed with SS, is reported. The following parameters were screened for the published cases of SS and CD association: demographic characteristics (gender, age), clinical features (clinical presentation of CD, SS and CD antibodies detection, genetic profile, histopathological patterns, the onset of symptoms and progression), therapy provided and response to this therapy.

3. Case Report

A 66 years old female patient who presented since 2014 with weight loss and iron deficiency anemia, was diagnosed as CD, based on symptomatology, positive anti tissue transglutaminase autoantibody and compatible intestinal pathology. Her blistering, papulovesicular, itchy, symmetrical and herpes-like cutaneous eruption was diagnosed as dermatitis herpetiformis, by the local dermatologist. Upon diagnosis, a gluten-free diet, dapsone and prednisone, were initiated. Associated conditions were hypertension and anxiety and she didn't comply with gluten withdrawal. Her past history revealed that In November 2013 she came to the local rheumatology clinic complaining of polyarthralgia, xerostomia and xerophthalmia. The Serological laboratory demonstrated positive ANA, anti-Ro/SS-A and rheumatoid factor of 118IU/mL. Anti-La/SS-B, anti-Sm, anti-dsDNA and anti-CCP were negative. Erythrocyte sedimentation rate was 46mm/1st hour, C-reactive protein (CRP) was 9.7mg/dL and electrophoresis showed hypergammaglobulinemia of 2.93mg/dL, vitamin D was 28ng/dL and hemoglobin 8.5g/dL. Serologies for hepatitis B and C, HIV were negative, but IgA anti-transglutaminase 56U/mL and IgA anti-endomysium 10 U/mL were positive. Schirmer test was <5mm in 5 minutes. She was treated with a gluten-free diet, prednisone 20mg/day associated with hydroxychloroquine 400mg/day and supplementation of vitamin D 1000IU/day and iron supplementation for 6 months. A good clinical response was noted along the years, with normalization of hemoglobin levels, CRP to 0,02mg/dL, vitamin D 45.1 ng/dL and negative results for anti-transglutaminase and anti-endomysium. During follow-up, a chest computed tomography was performed and showed interstitial pneumonia which was treated by azathioprine. Prednisone was completely tapered. Nowadays, she is feeling well, taking azathioprine 100mg/day and hydroxychloroquine 400mg/day. A nutritionist is following and encouraging her to keep a gluten free diet.

4. Results

The demographic, clinical and laboratory characteristics of the present patient with SS and CD, as well as, the other cases described in the literature review are summarized in Table 1.

Table 1. Clinical, demographical and treatment features of the studies regarding the association between Sjögren's syndrome associated with Celiac disease

Author, year	Type of study	N, age, gender	Diagnosis sequence, time	Clinical symptoms and histopathology	Autoantibody and genetic profile	Treatment	Improvement after therapy
[5] Caio et al., 2018	Observational	3/52, N/A, N/A	SS → CD	N/A	- Positive AE, AGA and ATTG	N/A	N/A
[14] Erbasan et al., 2017	Observational	1/82, 50yo, F	CD → SS	- Subjective and objective sicca syndrome and arthralgia - Positive salivary gland biopsy for SS: FS 1 - Positive intestinal histopathology for CD	- Positive AE and/or ATTG - Positive ANA, anti-Ro and anti-La	- Gluten-free diet	N/A
[15] Bibbò et al., 2017	Observational	6/255, N/A, F	CD → SS	N/A	N/A	- Gluten-free diet	N/A
[16] Lidén et al., 2007	Observational	1/20, N/A, N/A	SS → CD	- Positive intestinal histopathology for CD	- Positive AGA, AE, ATTG - HLA-DQ2+	N/A	N/A
[17] Szodoray et al., 2004	Observational	5/111, mean 39.8yo, 4F and 1M	SS → CD	- Abdominal discomfort (2/5), diarrhea (1/5), lack of appetite (1/5) and anemia (3/5) - Glandular swellings (1/5) and extra glandular manifestations (4/5) - Positive intestinal histopathology for CD	- Anti-Ro+ (5/5) - Anti-La+ (4/5) - ANA+ (4/5) - RF+ (4/5) - Positive CD antibodies, but did not specify	N/A	N/A

Author, year	Type of study	N, age, gender	Diagnosis sequence, time	Clinical symptoms and histopathology	Autoantibody and genetic profile	Treatment	Improvement after therapy
[18] Iltanen et al., 1999	Observational	5/34, mean 56.8yo, N/A	SS → CD	- Abdominal complaints (3/5), iron deficiency and anemia (1/5) - None had steatorrhea - Positive intestinal histopathology for CD - Increased intraepithelial CD3+ cells (4/5), αβ+ cells (2/5), γδ+ T cells (5/5), enhanced epithelial DR expression (5/5)	- IgA AE+ (3/5) - IgA AGA+ (4/5) - IgG AGA+ (1/5) - HLA-DQ2+	- Gluten-free diet	Yes CD improved No benefit on the sicca symptoms
[19] Khammassi et al., 2015	Case report	1, 41yo, F	CD → SS 33 years	- Sicca syndrome, polyarthritis, prolonged fever, lymphadenopathy - Positive salivary gland biopsy for SS - Cervical lymph node biopsy: no signs of malignancy - Positive intestinal histopathology for CD	- Positive ANA, anti-Ro, anti-La and RF	N/A	N/A
[20] Nikiphorou et al., 2014	Case report	1, 52yo, F	Simultaneous SS and CD	- Fatigue, diarrhea, weigh loss - Dry eyes, photosensitivity, pleuritic chest pains - Past of parotitis - Malar rash, bilateral conjunctival injection, vesicular rash - Positive salivary gland biopsy for SS - Rash biopsy: thrombotic capillaritis with neutrophilic exudate - Positive intestinal histopathology for CD Hypergammaglobulinemia, histopathology	- Positive ANA, anti-Ro, anti-La, RF and anti-cardiolipin IgM and IgG - ATTG >128 U/ml	- Gluten-free diet - Prednisolone 30mg/day, MP pulse, HCQ, AZA, MMF, RTX	Yes CD and SS improved after RTX
[21] Tinsa et al., 2010	Case report	1, 10yo, F	Simultaneous SS and CD	- Anemia, recurrent abdominal pain and short stature - Dry eyes - Schirmer + - Leukopenia, thrombocytopenia, hepatosplenomegaly and jaundice - She also had nodular regenerative hyperplasia of the liver - Positive intestinal histopathology for CD	- Positive AGA, ATTG, AE	- Gluten-free diet	Yes CD and liver dysfunction improved But maintained portal hypertension and mild anemia
[22] Katsikas et al., 2008	Case report	1, 62yo, F	SS → CD	- Eyes and mouth dryness - Schirmer and RB+ - Symmetric polyarthritis and polyneuropathy - Positive salivary gland biopsy for SS: FS 3 - Severe osteoporosis and vertebral fractures - Positive intestinal histopathology for CD - She also had cutaneous nodular amyloidosis, osteomalacia and myopathy	- Positive ANA, anti-Ro, anti-La and RF - Positive IgG-IgA AGA and IgA AE - HLA-DQ2+	- Gluten-free diet - Prednisolone, HCQ - Calcium and vitamin D	Yes Significant clinical and laboratory improvement
[23] D'Onofrio et al., 2006	Case report	1, 24yo, F	CD → SS 2 years	- Chronic diarrhea, abdominal pain, weight loss and iron deficiency anemia - Positive intestinal histopathology for CD - Xerostomia, xerophthalmia - Schirmer+ - Positive salivary gland biopsy for SS: FS 2	- Positive AE and AGA - Positive ANA, anti-La and RF	- Gluten-free diet - Methylprednisolone 4mg/day - Mebendazole	Yes Complete clinical, serological and histological recovery of CD Clinical e laboratory remission of SS with

Author, year	Type of study	N, age, gender	Diagnosis sequence, time	Clinical symptoms and histopathology	Autoantibody and genetic profile	Treatment	Improvement after therapy
				- She also had ascariasis			decrease of all autoantibodies after anti-parasitic therapy and discontinuation of estrogen therapy
[24] Fracchia et al., 2004	Case report	1, 45yo, F	SS → CD 18 years	- Xerostomia, xerophtalmia and arthralgia - Schirmer+ - Positive salivary gland biopsy for SS - Diarrhea, weight loss, fatigue, angular stomatitis, anemia and reduced bone mineral density - Positive intestinal histopathology for CD - She also had PBC, hyperthyroidism and tubular renal acidosis	- Positive anti-Ro, anti-La and RF - AE+ - Anti-mitochondrial+ - Positive anti-thyroglobulin, anti-TPO and anti-TSH receptor - HLA-DQ2+	- Gluten-free diet - Prednisone 10-25mg/day - Tauroursodeoxycholic acid 500mg/day - Alendronate 10mg/day - Ialuronic acid eye-drops - Potassium citrate 6g/day - Calcium - Thyroidectomy	Yes CD improved But no significant changes in liver enzymes and renal function
[25] Kaufmann et al., 1998	Case report	1, 26yo, F	Simultaneous CD and SS 15 years after dermatitis herpetiformis	- Diarrhea, anemia and dermatitis herpetiformis - Positive intestinal histopathology for CD - Sicca syndrome and polyarthritis - Positive Schirmer, RB and salivary scintigraphy - Positive salivary gland biopsy for SS: FS 1	- Positive ANA, anti-Ro and anti-La - AE+ - HLA-DQ2+	- Gluten-free diet - Prednisolone, sulfasalazine, dapsone and HCQ	Yes CD manifestations and polyarthritis improved
[26] Whitehead et al., 1987	Case report	1, 44yo, F	Simultaneous CD and SS	- Iron deficiency anemia, pruritus and weight loss - Positive intestinal histopathology for CD - Sicca syndrome - Renal tubular acidosis - Schirmer+ - She also had hypokalemic myopathy due to RTA and primary biliary cirrhosis	- Negative AGA - Positive anti-mitochondrial	- Gluten-free diet - Methylcellulose eyedrops - Sodium bicarbonate - Potassium supplementation and alkalis - Iron therapy	Yes CD and SS improved
[27] Maclaurin et al., 1972	Case report	1, 73yo, F	CD -> SS	- Diarrhea, intermittent vomiting, abdominal distension and increased flatulence - Treatment for “rickets” for several years as a child - She also had megaloblastic anemia and hypothyroidism - Positive intestinal histopathology for CD - Dry eyes and mouth - Schirmer+	- Negative ANA and RF - Positive anti-TPO and anti-thyroglobulin	- Gluten-free diet - Vitamin B injection, folic acid, calcium and other vitamins - Thyroxine	Yes CD improved Partial improvement of sicca syndrome
[28] Pittman et al., 1965	Case report	1, adult, N/A	SS → CD	- Nutritional deficiencies and diarrhea - Functional test+ - Positive intestinal histopathology for CD	N/A	- Gluten-free diet	Yes CD improved
Silvar et al., 2020*	Case report	1, 66yo, F	CD → SS	- Weight loss, iron deficiency anemia and dermatitis herpetiformis - Positive intestinal histopathology for CD - Sicca syndrome, polyarthralgia and interstitial pneumonia - Schirmer+	- Positive ANA, anti-Ro and RF - Positive IgA ATTG and IgA AE	- Gluten-free diet - Dapsone - Prednisone, HCQ, AZA	Yes CD and SS improved

AE: anti-endomysium, AGA: antigliadin antibody, ANA: antinuclear antibodies, ATTG: anti-tissue transglutaminase, AZA: azathioprine, ANA: antinuclear antibody, CD: celiac disease, F: female, FS: focus score, HCQ: hydroxychloroquine, M: male, MMF: mofetil mycophenolate, MP: methylprednisolone, N/A: not available, RTA: renal tubular acidosis, RB: rose Bengal, RF: rheumatoid factor, RTX: rituximab, SS: Sjögren's syndrome, TPO: thyroid peroxidase, yo: years old, +: positive, * present study.

Reviewing the international literature from 1966 to 2020, only 16 studies describing 31 patients with SS associated with CD were reported [5,14-28]. There are 6 observational studies and 10 cases reports. Adding the present case report increased the number mount to a total of 17 studies with 32 patients.

In relation to demographics, the age varied from 10 to 73 years old, with a median of 45 years and the great majority are female (21 out of 32). In 10 cases, some of the data are missing. SS preceded CD manifestations in 7 studies, CD was the first presentation in 6 articles and simultaneous diseases was observed in 4 reports. Whenever data were available, time between the two diseases varied from 2 to 33 years.

Regarding the clinical manifestations, in 12/17 studies the patients presented signs and symptoms of CD and SS simultaneously, most of them had sicca syndrome (11/17) and 7/17 had diarrhea. There was no information regarding this topic on 2/17. Autoantibodies related to SS showed that anti-Ro and anti-La were positive in 8/17 studies, while CD-related antibodies were positive in 12/17 studies: 9 with endomysial, 6 with gliadin and 5 with tissue transglutaminase antibody's positivity. With respect to the genetic profile, HLA-DQ2 alleles were found in 5 studies. Regarding therapy, the majority received a gluten-free diet for the CD treatment (13/17 studies, in 4 reports, data were not available). Glucocorticoid was prescribed in 6/17 studies, hydroxychloroquine in 4/17 and in only 3/17, other immunosuppressive agents were used. When described, all studies demonstrated improvement of CD manifestations (11/17), 7/17 improved SS symptoms and in 6/17 response of therapy was not clear.

5. Discussion

The present narrative review is the first reported literature screen on SS cases associated with CD. To our knowledge, the triple association of SS, CD and dermatitis herpetiformis was never described, only SS associated CD were searched. The first to report SS and CD association was Pittman and Holub in 1965 [28] and since then, additional 32 patients are herein reported. Long-life gluten-free diet is the only specific nutritional therapy for CD. Indeed, in all patients, presently reviewed, gluten was withdrawn with a very good outcome. One should bear in mind that gluten might be toxic, not only to CD patients [29], that gluten free diet has its side effects [30] and the nutrient withdrawal might be problematic [31,32], thus, mirroring the present patient's compliance difficulties. Both CD and SS are autoimmune conditions and as such, the patients are at risk to acquire additional autoimmune disease, along their life-cycle, thus fitting into the autoimmune puzzle [1,3,4,11,12,13,33]. The presented women fit into the well described entity of multiple autoimmune syndrome, characterized by three or more autoimmune disorders in a same individual [4,12]. Multiple autoimmune syndromes are subdivided into three types. Type 2 contains SS, while SS and dermatitis herpetiformis are included in type 3 [4]. It is suggested that the present case might be part of type 3, since it includes 2/3 of her autoimmune diseases. Interestingly, 15% of patients with SS also have biopsy proven CD meaning that the latter is far more common in SS patients than in the general population [16]. Furthermore, CD is more prevalent in p primary SS vs controls (6.78% vs 0.64%, $p < 0.0001$) [34]. If substantiate, most probably the 32 cases described in here, represents underdiagnosis of the SS and CD linked association.

The pathophysiological mechanisms presenting SS, CD and dermatitis herpetiformis in the same patient, is quite challenging. Dermatitis herpetiformis is a gluten related condition frequently associated with CD and is part of the gut-skin axis. It was suggested that gut microbiota with its vast mobilome and circulating gluten/ gliadin peptides are potential important actors along the gut-skin axis [35,36]. Metabolites from either the diet or the enteric microbiota might be skin accessible. Posttranslational modifications of naïve intestinal luminal proteins, enteric horizontal gene transfer of hostile auto-immunogenic genes, increased intestinal permeability resulting in the leaky gut and many blood/lymph circulating and activated immune cells, cytokines, lymphokines might reach the skin or alternatively the body's moisture-producing glands inducing SS pathologies [11,35-39]. Another brainstorming aspect is the tissue transglutaminase enzyme, a well-known pleiotropic enzyme that is localized in all human organs, including CD intestine, skin, joints, endocrine and salivary glands [37,40-44]. Intriguingly, anti tissue transglutaminases are part of the proteome secreted in the saliva of primary SS patients [45]. So, multiple pathways can transmit the luminal autoimmune messages\signals to peripheral organs to induce poly-autoimmunopathy [11,36,39].

It is suggested that detailed gastrointestinal history, complaints and examination should be performed in SS patients due to the present observation that the majority of the SS cases precedes CD diagnosis. More so, subtle gastrointestinal symptoms or the presence of subclinical alterations such as iron deficiency anemia, osteoporosis, weight loss or any CD associated extraintestinal manifestations may draw attention to subclinical CD. To obtain the correct diagnosis of CD, CD-related autoantibodies profile is required. If they are positive, then endoscopy with small intestinal biopsy is necessary. It should be stressed that the follow-up of these patients with correct dietary restrictions to avoid morbidity, complications and even mortality when treated appropriately, is crucial [46]. In contrast, CD patients complaining of sicca syndrome, parotid enlargement, hypergammaglobulinemia or the presence of systemic manifestations such as purpura, neuropathy, lung disease or renal tubular acidosis should suggest the presence of SS. In such a case, Schirmer and Rose Bengal, aside from salivary gland test and autoantibodies (anti-Ro and anti-La) should be checked.

The strengths of this article are the inclusion of all case reports of SS and CD which were published in the literature. The limitations are: no genetic analysis for CD and SS were performed and dermatitis herpetiformis was diagnosed on clinical presentation and good response to dapsone, but no skin biopsy was performed. Some cases published in other foreign Languages could have been missed.

In conclusion, this is the first comprehensive review of the association between SS and CD. More awareness on the association will diagnose more patients with the hope to decrease disease activity, attenuate morbidity and prevent associated complication.

Abbreviations

CD- celiac disease, SS- Sjögren's syndrome

Conflicts of Interest

None of the authors has conflict of interest and the study was not granted.

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Take Home Messages

1. Sjögren's syndrome is an autoimmune exocrinopathy characterized by sicca syndrome (eyes and mouth dryness) associated with systemic involvement.
2. Celiac disease is an autoimmune disease characterized by gluten intolerance.
3. There are few cases described in the literature on the unique association of SS and CD in the same patient. Most probably the association is under-detected. The CD, SS and dermatitis herpetiformis was not described in the same patient.

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