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## Case Report

# Metabolic Disorders in a Cohort of Patients with Sjogren's Disease

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**Abstract:** Disorders of metabolism have been seen in multiple autoimmune diseases including SLE and Sjogren's disease. The current studies were designed to evaluate mutations in genes involved with metabolism in a cohort of patients with Sjogren's disease diagnosed from clinical criteria and the presence of antibodies to salivary gland antigens. Patients included in these studies met criteria for Sjogren's disease and were able to get genetic studies. There were 194 of these patients and 192 had mutations in one or more gene involved with metabolism: 188 patients had mutations in mitochondrial respiratory chain genes, 17 patients had mutations in mitochondrial tRNA genes, 10 patients had mutations in mitochondrial DLOOP regions, 6 patients had mutations involved with carnitine transport, 6 patients had mutations in genes causing mitochondrial depletion and 7 patients had glycogen storage diseases. In all cases, treatment of the metabolic disorder led to symptomatic improvement in energy, exercise tolerance, gastrointestinal dysmotility and management of infections. In conclusion, metabolic disorders are common in patients with Sjogren's disease and may be one of the factors leading to the initiation of the disease. Treatment of patients with Sjogren's disease should include treatment of the underlying / associated metabolic disorder.

**Keywords:** Sjogren's disease; metabolism; autoantibodies

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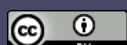
## 1. Introduction

Understanding of the pathophysiology of autoimmune diseases has been rapidly advancing in the last several years. While dysregulated immune function has been appreciated for decades, appreciation of dysregulated metabolism in autoimmune diseases is relatively recent [1–7]. Abnormal mitochondrial function was first observed in SLE [8–15] but has been observed in Sjogren's disease as well [16–26]. We observed that many of the symptoms attributable to Sjogren's disease were in fact related to the underlying metabolic disease in particular patients. We therefore sought to determine the number of patients with mutations in genes associated with metabolism in a cohort of patients with Sjogren's disease seen in our clinics.

## 2. Results

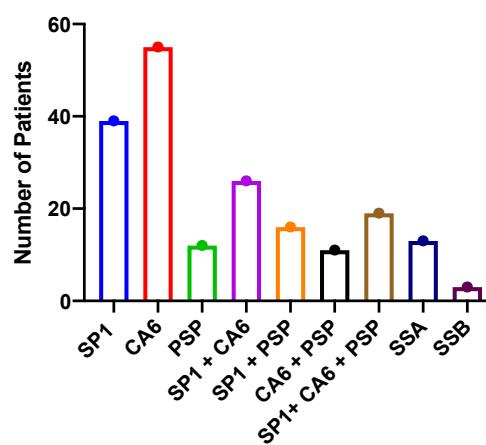
The first issue to address is the autoantibodies expressed by the patients in this study. They all met American – European clinical criteria for Sjogren's disease with clinical signs of dry eye and dry mouth and positive Schirmer's tests, except only 13 of the patients had SSA antibodies. All the patients had autoantibodies associated with Sjogren's disease, but the majority had antibodies to SP1 and CA6 (Figure 1), which are salivary gland specific antigens [27–30]. Many of the patients expressed more than one autoantibody. Interestingly, 54% of the patients with SP1 autoantibodies expressed IgM autoantibodies while 67% of the patients with CA6 autoantibodies expressed IgG autoantibodies. These patients might be called seronegative Sjogren's patients by some investigators because of their lack of SSA expression.

Genetic studies looking for metabolic disorders were done on these patients because of symptoms that are consistent with adult- onset metabolic disorders: fatigue, exercise intolerance,

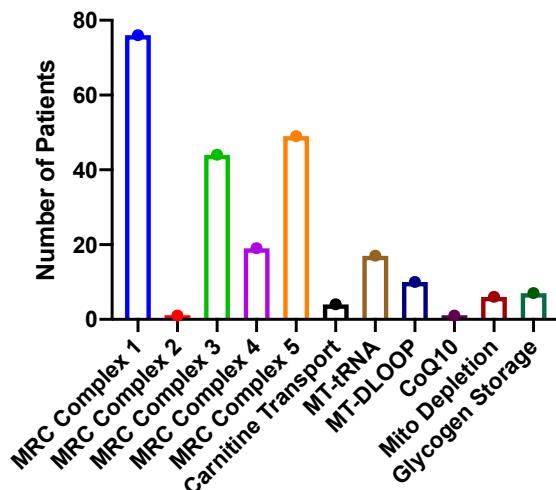


recurrent infections, accelerated osteoarthritis, gastrointestinal dysmotility including gastroparesis, gastroesophageal reflux and constipation and in some cases dyspnea. In all cases, whole exome sequencing and sequencing of the mitochondrial genome was performed by GeneDx. Of the patients studied, 192 (99%) had mutations in genes associated with metabolic function (Figure 2). Some patients carried more than one mutation. Rare missense mutations in mitochondrial respiratory chain genes were common: complex 1 – 76, complex 3 – 44, complex 4 – 19 and complex 5 – 49. One patient had a mutation in the succinate dehydrogenase gene, which is involved with complex 2 of the mitochondrial respiratory chain but also the citric acid cycle. Six patients had mutations associated with carnitine: CPT2 – 4 and SLC22A5 – 2. Mutations in various mitochondrial tRNA were seen in 17 patients and 10 patients had rare MT-DLOOP mutations. One patient had a PDSS2 mutation associated with CoQ10 deficiency, and 6 patients had mutations associated with mitochondrial depletion syndrome: POLG – 3, MCME1 – 1, RRMP8 – 1 and thymidine kinase – 1. Seven patients had mutations in genes causing glycogen storage diseases: Pompe disease – 1, Forbes – Cori disease – 1, McArdle's Disease -1, phosphofructokinase deficiency (type IX) – 1 and lactate dehydrogenase deficiency (type XI) – 3. The result in all these mutations is inefficient generation of ATP and in the case of the glycogen storage diseases, difficulty handling complex carbohydrates.

The treatment of mitochondrial disorders involves several medications, each of which works by a different mechanism, so a synergistic effect is seen [31]. The first medication is CoQ10, which is involved with transporting electrons between complex 1 and 3 of the mitochondrial respiratory chain and helps generate ATP more efficiently [32,33]. Creatine generates ATP through the creatine phosphate shuttle and discourages replication of abnormal mitochondria [34]. Carnitine brings fatty acids into the mitochondria so they can undergo beta oxidation to generate NADH [26,35]. Folic acid is a co-factor for several respiratory chain enzymes [36]. N-acetyl cysteine is a potent antioxidant [37,38] and the amino acid glutamine acts as an alternative energy source [39,40]. The doses of these medications vary for individual patients, but all patients have noted some benefit from them with regards to fatigue, exercise tolerance and decreasing infection rate. With regards to the glycogen storage diseases, patients are taught to avoid complex carbohydrates and supplement with simple sugars [41–46]. At the same time, since glycogen storage diseases are generally associated with mitochondrial dysfunction, we usually add the medications listed above that are used to treat mitochondrial diseases [47,48]. These patients saw significant improvement in fatigue and exercise tolerance with this regimen.



**Figure 1.** Autoantibodies Identified in Patients in this Study. Figure Legend: This figure demonstrates the number of patients with particular autoantibodies included in this study. SP1 = salivary protein 1, CA6 = carbonic anhydrase 6, PSP = parotid secretory protein, SS = Sjogren's syndrome.



**Figure 2.** Mutations in Genes Involved with Metabolism in Patients with Sjogren's Disease. Figure Legend: This figure demonstrates the number of patients with particular mutations in genes involved with metabolism. MRC = mitochondrial respiratory chain. MT = mitochondrial. Mito depletion genes included POLG, MCME, RRMP8 and thymidine kinase. Glycogen storage diseases included Pompe, Forber – Cori, McArdle's, phosphofructokinase deficiency and lactate dehydrogenase deficiency.

### 3. Discussion

We have demonstrated in this study that Sjogren's patients with symptoms consistent with a metabolic disorder, fatigue, exercise intolerance, gastrointestinal dysmotility and recurrent infections, often have mutations in genes important for metabolism. The identification of the metabolic disorder is helpful in suggesting therapies to improve disease symptoms. It is certainly true that all these patients come from a clinic that specializes in metabolic disorders so there is some bias regarding patient selection. Interestingly, when patients with metabolic disorders are evaluated as a group there is a very high incidence of Sjogren's disease [26,49].

Mitochondrial dysfunction has been observed in patients with Sjogren's disease by several investigators [16,17,21,22,50–52]. The question becomes whether mitochondrial dysfunction occurs secondary to the inflammation in the salivary glands or whether it is a primary process contributing to the development of the disease. One way that mitochondrial dysfunction could contribute to disease pathogenesis is by decreasing the ability to handle infections thus leading to more tissue damage and the increased likelihood that normal autorecognition is turned into pathologic autoreactivity [53–56]. Mitochondrial dysfunction could lead to modification of various proteins and other molecules involved with signaling and genetic function [56]. Alternatively, inefficient mitochondrial function could lead to reliance on glycolytic metabolism, which tends to encourage the actions of effector rather than regulatory lymphocytes and other immune cells [57–64]. Interestingly, IL-14 (a-taxilin) was recently shown to stimulate glycolysis [65]. The IL-14 transgenic mouse has been shown to be an excellent model for Sjogren's disease [66,67]. Recent studies have demonstrated that blocking glycolysis inhibits the development of Sjogren's disease manifestations in this animal model [68].

This manuscript has weaknesses because it describes patients followed as part of normal clinical service and does not describe a research study designed to address a particular research question. Furthermore, while all of the patients had autoantibodies associated with Sjogren's disease, only a few patients had SSA antibodies, which are the only autoantibodies in the official America – European diagnostic criteria for Sjogren's disease [69]. Nonetheless, these patients all met the necessary clinical criteria and demonstrated autoreactivity by the presence of autoantibodies directed towards salivary and lacrimal gland antigens – the diagnostic criteria may have to expand to include additional autoantibodies. Furthermore, expression of SSA versus SP1/CA6/ PSP may denote

different stages of disease and/or different types of Sjogren's disease that are driven by different metabolic and immunologic abnormalities [27,66,68,70–72].

Whether metabolic abnormalities are a primary or secondary function in patients with Sjogren's disease, treatment based on these abnormalities is helpful for the patients symptomatically and may lead to other new forms of therapy.

## 4. Materials and Methods

### 4.1. Patients

All the patients discussed in this manuscript were followed in the Immunology clinics of SUNY at Buffalo School of Medicine. They had clinical symptoms of xerostomia and xerophthalmia with positive Schirmer's tests performed by their Ophthalmologists. Some patients had demonstration of decreased salivary flow. All patients had serologic testing for antibodies to SSA, SSB, salivary gland protein 1 (SP1), carbonic anhydrase 6 (CA6) and parotid secretory protein (PSP) as part of their routine medical care. Because all patients had complaints of fatigue, exercise intolerance, accelerated osteoarthritis and recurrent infections, genetic studies were obtained as part of their routine medical care. Twenty-seven percent of the patients had associated gastrointestinal dysmotility. The patients ranged in age from 21-81 years (mean 54.2 +/- 13.5 years). Eighty-nine percent of the patients were female.

### 4.2. Genetic Studies

Sequencing of the mitochondrial genome and whole exome sequencing was performed by GeneDx (Gaithersburg, MD).

## 5. Conclusions

Patient with Sjogren's disease frequently have an underlying metabolic disorder that is responsible for some of the symptoms attributed to the disease. Treatment of the metabolic disorder leads to symptomatic improvement in the patients.

**Author Contributions:** Julian L. Ambrus Jr., took care of the patients, obtained the genetic studies and wrote the paper. Alexander Jacob helped with autoantibody analysis and reviewed the paper. Abhay Shukla performed the autoantibody studies and reviewed the paper.

**Funding:** These data were obtained from routine clinical care. No external funding was utilized.

**Institutional Review Board Statement:** The data were obtained from routine clinical care and did not involve identification of individual patients. No IRB approval was required.

**Informed Consent Statement:** The data were obtained from routine clinical care and did not involve identification of individual patients. No informed consent was required..

**Data Availability Statement:** All the data are included in this manuscript.

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**Conflicts of Interest:** None of the authors had any conflict of interest.

## Abbreviations

The following abbreviations are used in this manuscript:

CA6 = carbonic anhydrase 6

SP1 = salivary gland protein 1

PSP = parotid secretory protein

SSA = Sjogren's syndrome A = anti – Ro  
SSB = Sjogren's syndrome B = anti- LA  
ATP = adenosine triphosphate

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