

Literature review: the prevalence and indicators of sjögren's syndrome in juveniles

Jamie Smolik¹, Rob Taylor², Victoria Wilson¹, Margaret Weber¹, Iquebal Hasan³, Ershal Harrison², and Madeline Aulisio²

¹University of Kentucky, College of Dentistry Lexington, Kentucky, KY 40513, USA

²Associate Professor/Team Leader, University of Kentucky, College of Dentistry Lexington, Kentucky, KY 40513, USA

³Assistant Professor/ Division Chief, ECU School of Medicine, USA

Abstract

Sjögren's Syndrome (SS), a chronic auto-immune disorder most frequently diagnosed in women over the age of 40, is becoming progressively more evident in juvenile patients. Coupled with the fact that there is no set diagnostic criteria for diagnosing SS in the pediatric population and the finding that SS manifests differently in pediatric and juvenile patients than in adults, diagnosis in younger patients is often difficult. This review seeks to address this situation by examining proposed diagnostic criteria, advances made in identifying diagnostic markers for juvenile Sjögren's Syndrome, and viable treatment methods for both primary and secondary SS. Although a wide spectrum of possible manifestations of juvenile SS as well as its low prevalence may complicate research studies, the knowledge gained will serve to better organize future research while assisting clinicians and benefiting patients.

Introduction

Sjögren's Syndrome (SS) is a chronic auto-immune disorder that is most frequently diagnosed in women over the age of 40 and involves both glandular and extra-glandular systems. It frequently affects the salivary and lacrimal glands and is characterized by the triad of xerostomia, keratoconjunctivitis sicca and the presence of various auto-antibodies [1]. A common manifestation of SS is damaged salivary glands, which hinders saliva production and quality. This change in saliva frequently causes increased dental caries, stomatitis and candidiasis, all of which can contribute to a patient's diminished quality of life [2].

Epidemiology

Sjögren's syndrome is a chronic, systemic autoimmune disease. It is known to infiltrate the exocrine glands. In SS, the white blood cells attack the glands which primarily produce tears and saliva. As a result, most Sjögren's patients will present with oral and optical dryness. The challenge in diagnosing and treating patients with SS is that no two patients have identical symptoms. Additionally, it can present as a primary or secondary disease.

In primary Sjögren's, signs and symptoms are not dependent on the presence of another disease; however, in secondary Sjögren's Syndrome, the symptoms present in conjunction with another autoimmune disease – such as lupus or rheumatoid arthritis [3].

Sjögren's Syndrome is thought to be one of the top three most common systemic autoimmune diseases. According to the Sjögren's Syndrome Foundation (2014) [4], there are 4,000,000 people in the United States affected by SS. It is difficult to determine the exact number of affected individuals due to the limited amount of published studies. Even within the same geographical area, the estimated occurrence of SS can vary drastically due to the classification standards used. Therefore, SS often goes undiagnosed or misdiagnosed because the symptoms

of SS can overlap the symptoms of many other more prominent autoimmune diseases [3].

While Sjögren's Syndrome commonly affects middle-aged women, the incidence of juvenile SS is becoming progressively more evident. One-hundred and forty-five cases of primary juvenile SS have been recorded in international pediatric literature. However, only five percent of adult SS patients indicated having reported symptoms before the age of twelve. Juvenile Sjögren's affects more females than males at a ratio of 7:1. The mean age for juvenile SS onset is 10 years of age. Various ethnic groups have similar prevalence rates to those recorded in the United States. Adult and juvenile SS symptoms present similar to many other autoimmune disorders; therefore, many cases of juvenile SS go undiagnosed. Unlike adult SS, however, juvenile SS presents with more frequent parotid swelling and fewer sicca symptoms [5].

Classification

Historically, SS has been a disease that was thought to arise in adulthood; however, cases of SS arising in juvenile patients are being diagnosed more frequently. Patients who develop SS during adolescence show different manifestations of the disease than adult patients, making identification and diagnosis of the disease challenging. In some patients, diagnostic markers for SS have been detected in the blood serum of patients who are asymptomatic, and have therefore been diagnosed with subclinical SS. Furthermore, as with SS in adults, juvenile SS can be primary or secondary. In primary SS, there is no

Correspondence to: Iquebal Hasan, Chief/Assistant Professor-Oral Medicine, ECU School of Dental Medicine, KY 40513, USA, Tel: 252-737-7158; E-mail: hasani16@ecu.edu

Key words: Juvenile, Sjogren's Syndrome, manifestations, diagnosis

Received: February 17, 2017; **Accepted:** March 07, 2017; **Published:** March 10, 2017

associated autoimmune disease and the underlying cause for SS is unknown. In secondary SS patients have an underlying autoimmune disease, such as rheumatoid arthritis, and SS arises secondary to this disease.

Clinical manifestations

There is strong evidence that shows that recurrent parotitis in juvenile patients is a common clinical manifestation of primary juvenile Sjögren's Syndrome. Basziz *et al.* [6] report that while parotitis is common in childhood, laboratory diagnostic tests should be ordered in children with recurrent parotitis to determine if the child has SS. Further support comes from Singer *et al.* [7], who suggest that parotitis may be the most common glandular manifestation seen in pediatric primary SS, with other reports citing an occurrence of up to 75% of cases. Longhi *et al.* [8] also support this conclusion and argue that recurrent parotitis should be included as a diagnostic factor for juvenile SS. Alp *et al.* [9] reported on a child diagnosed with primary SS who presented with 15 episodes of parotid swelling over the course of 4 years, with each episode lasting 1-2 weeks, supporting the idea that recurrent parotitis may be indicative of SS. It is important to keep in mind, however, that isolated parotitis is commonly seen in pediatric patients and can be associated with viral or bacterial infections, but that recurrent infection may indicate an underlying etiology such as SS [6,9]. In addition to this case report, there have been other reports supporting the idea that parotitis can occur years before other symptoms of SS, and may be a good first indication of juvenile primary SS [10].

Tomiita *et al.* [11] conducted a study in which they distributed questionnaires to hospitals, and received back 61 cases of juvenile SS from 1290 hospitals. The patients were separated between primary and secondary SS, and then the primary SS patients were then further divided into clinical (presence of dry mouth or dry eyes at time of diagnosis) or subclinical (absence of dry mouth or dry eyes at time of diagnosis). 75% of the patients in this study with primary SS fell into the subclinical category. The results of their study suggest that in primary SS, the same immunological characteristics are seen among both the clinical and subclinical groups [11]. They also report that patients in the clinical group more frequently displayed sialogram abnormalities and decreased lacrimal gland excretion (tested via Schirmer's test and the Rose-Bengal test). However, these abnormalities were also seen in the subclinical group. Based on this finding, Tomiita *et al.* [11], suggest that with the exception of experiencing dryness, there are no differences between the clinical and subclinical groups. Furthermore, because the feeling of dryness is subjective, it is not a reliable or universal indicator of juvenile SS [11]. Their study supports the argument that because a significant number of patients with primary SS have no symptoms of dryness, other diagnostic criteria besides sicca symptoms are needed for an accurate diagnosis [11-13]. It was found that patients in the subclinical group presented with mostly systemic symptoms (fever, exanthema, and arthralgia) which may be more useful in making a diagnosis. Finally, laboratory tests show that antinuclear antibodies, elevated serum IgG, rheumatoid factor, anti-Ro/SS-A antibodies and anti-LdSS-B antibodies were observed in both groups [11].

Although glandular symptoms more commonly present in patients with primary SS, extra-glandular symptoms can also be present, and therefore should be checked for in suspected SS patients. Some of the extra-glandular manifestations associated with primary SS include CNS involvement, thyroiditis, nephritis, renal tubular acidosis, arthralgia, arthritis, Raynaud's phenomena, chronic interstitial pneumonitis, myositis and vasculitis have been reported and can be life-threatening

if not treated [14,15]. Support for CNS involvement comes from a case report by Ohtsuka *et al.* [16], which describes a 9 year old child who presented to a hospital with hemiparesis. The report explains that the diagnosis of primary SS was made and while it is not seen commonly in patients with SS, CNS involvement in primary SS is possible and should be kept in consideration during diagnosis. Another study by Kobayashi *et al.* [1] reported on 4 cases of juvenile SS which were complicated by other factors. They reported that two children diagnosed with primary SS had a renal biopsy which revealed interstitial nephritis, while another patient they reported on experienced severe headache and slightly elevated CSF cell count, representing another incidence of CNS involvement in childhood SS [11].

It is known that adult onset primary SS can occasionally have renal manifestations, but it is not seen as frequently in juvenile patients. Two extra-glandular presentations that literature has frequently described in patients with primary SS are nephritis and renal tubular acidosis. An example of nephritis is described in a case report by Igarashi *et al.* [17]. They described a patient who first presented with recurrent parotitis at the age of 5, was diagnosed with primary SS at the age of 10 and developed interstitial nephritis at the age of 12. Another case, which was reported by Bogdanović *et al.* [18], describes a teenage girl who developed renal tubular acidosis and tubule-interstitial nephritis secondary to primary SS.

Renal tubular acidosis is a well-known complication of adult onset SS, but literature is now beginning to recognize this complication in juvenile patients as well. A retrospective study and literature review was done by Pessler *et al.* [19], and they identified 12 cases of juvenile SS since 1993 that were complicated by renal tubular acidosis. They stated that RTA is associated with primary SS, but it was not determined if this relationship was causal or an association. The authors of the article argue that RTA is an under recognized complication of SS, and RTA can be life threatening if not treated. However with early diagnosis and appropriate treatment, it generally has a good prognosis [19].

Diagnosis

To date, there is not much information on juvenile onset of SS. As a result, there is no standardized diagnostic criteria, making diagnosis challenging. It is known that anti-Ro/SS-A and anti-La/SS-B antibodies can be used as SS markers in adult patients, however 26% of juvenile SS patients show negative results for both antibodies, making their diagnostic capability of limited value in pediatric patients [12]. A Schirmer's test, Rose- Bengal staining or sialography can also be useful in diagnosis, but sometimes these tests are not enough for a confirmed diagnosis. While there are some guidelines for diagnosing adult onset SS, there is less information available to help clinicians diagnose juvenile onset SS [20]. Houghton's *et al.* [14] suggest that the American-European Consensus Group's (AECG) classification criteria for SS in adults is not a valid criteria for juveniles because sensitivity in the juvenile population is low. There is evidence from multiple studies that suggests recurrent parotitis is an early manifestation of PSS and should be considered for diagnostic criteria [6,12,14]. Houghton *et al.* [14] study suggests that inclusion of recurrent parotitis increased the sensitivity of the proposed pediatric criteria by Bartunkova *et al.*, again supporting the idea that recurrent parotitis is an early manifestation of juvenile PSS. Additionally, Houghton *et al.* [14] stated that the AECG criteria are not sensitive enough to apply to pediatric patients because of the lack of clinically identifiable symptoms present in many pediatric patients. Bartunkova *et al.* [20] recognized this discrepancy, and in 1999 proposed a new set of diagnostic criteria for pediatric patients, as seen in Table 1, although his proposal has not yet been accepted.

Table 1. Bartunkova's proposed diagnostic criteria for juvenile patient's with Sjogren's Syndrome

<p>I. Clinical Symptoms</p> <ol style="list-style-type: none"> 1. Oral: Recurrent parotitis or enlargement of parotid gland. 2. Ocular: Recurrent conjunctivitis without obvious allergic or infectious etiology, keratoconjunctivitis sicca. 3. Other mucosal: recurrent vaginitis 4. Systemic: <ol style="list-style-type: none"> a) fever of unknown origin b) non-inflammatory arthralgias c) hypokalemic paralysis d) abdominal pain <p>II. Immunological abnormalities: presence of at least one of the following antibodies:</p> <ol style="list-style-type: none"> 1. Anti-SS-A 2. Anti-SS-B 3. High titer of ANA (speckled type) 4. Rheumatoid factor <p>III. Other laboratory abnormalities or additional investigations</p> <ol style="list-style-type: none"> 1. Biochemical: elevated serum amylases (parotid isoenzyme, pancreatic isoenzyme or both.) 2. Hematological: leukopenia, high ESR 3. Immunological: polyclonal hyperimmunoglobulinemia 4. Nephrological: renal tubular acidosis (incapacity of spontaneous or challenged acidification of urine) 5. Histological proof of lymphocytic infiltration of salivary glands or other organs (i.e. liver biopsy) 6. Objective documentation of ocular dryness (Bengal red staining or Schirmer test) 7. Objective documentation of parotid gland affection (sialography) <p>IV. Exclusion of all other autoimmune diseases</p>

According to the Revised International Classification Criteria for Sjögren's Syndrome from the American-European Consensus Group, primary SS can be diagnosed in adults if four of the following six criteria are present: presence of ocular symptoms, presence of oral symptoms, evidence of keratoconjunctivitis sicca, focal sialadenitis upon minor salivary gland biopsy, instrumental evidence of salivary gland involvement and presence of SSA or SSB antibodies [8]. This criteria, however, often does not provide an accurate diagnosis for juvenile SS since the symptoms seen in juvenile SS vary. For example, Kobayashi *et al.* [12] and Tomiita *et al.* [11] report that up to 75% of juvenile SS patients do not present with sicca symptoms, but have similar pathological and laboratory findings as adult cases.

Significant advances have been made in identifying diagnostic markers for juvenile primary SS. Kobayashi *et al.* [12] conducted a study of 7 juvenile patients with SS (primary or secondary) in which they used immunoblot analysis of sera to detect α -fodrin, an auto antigen that is associated with adult primary SS. The results of this study found that the sera of all 7 patients with primary SS was positive for anti- α -fodrin antibody as well as 2 of the 4 patients with secondary SS and 1 of the control patients with SLE alone. α -Fodrin is a subunit of cytoskeleton and is cleaved to form a 120kDa fragment which is abundant in salivary glands. They also suggest that SS without sicca symptoms is an early stage of the disease [12]. Additional evidence of use of anti- α -fodrin antibody as a diagnostic tool comes from a study by Shiari *et al.* [21] which suggests that there may be distinct epitopes of anti- α -fodrin autoantibody that could possibly help to distinguish between primary and secondary SS.

A second study by Maeno *et al.* [13] provides support for the use of anti- α -fodrin as a diagnostic marker for juvenile SS. Again, using Western blot analysis, they analyzed the serum of 15 juvenile patients with SS (11 had primary and 4 had secondary) and 16 patients with

systemic lupus erythematosus. The results of their study showed that all 15 SS patients had anti- α -fodrin reactivity, but only 2 of the 16 patients with SLE showed reactivity. However, it should be noted that these two patients could have secondary SS and they were never tested for SS during the time of the study. They also reported that in comparison to adult SS, juvenile patients reported fewer dryness symptoms [13]. 26.7% of participants with SS in this study reported symptoms of xerophthalmia or xerostomia. However, objective examination for dryness via Schirmer and Rose-Bengal tests and salivary flow rates showed abnormal results in 40%. They also found that 66.7% of patients with SS had enlarged salivary glands [13]. This study provides additional support for the idea that even though the clinical presentation is different, there is a similar pathogenesis between juvenile and adult onset SS [11-13]. The results of this study are in agreement with others about the idea that juvenile onset SS is the early stage of adult onset SS [12,13]. Additional support comes from Tomiita *et al.* [11] whose study showed that seven patients (out of 32) who began with subclinical SS proceeded to develop clinical SS.

Another possible diagnostic marker for juvenile SS is tumor necrosis factor alpha (TNF α). TNF α blockade has been shown to be ineffective in treating the glandular and extraglandular manifestations of adult SS. However, Pessler *et al.* [22], describe a case report in which a child diagnosed with SS at the age of 11 responded beneficially to TNF α blockade. The study reports that the child's arthritis significantly improved, however, none of her other SS symptoms improved. The authors of this study suggest that the patient may have SS secondary to JRA which would explain the results, but it is also possible that the child has primary SS because uveitis and arthritis have been observed in other pediatric patients. Pessler *et al.* [22] state they support the second theory because the patient presented with purpura at 8 months of age, along with caries in the primary dentition and optic neuritis,

all of which suggest a very early onset of primary SS. The authors of this study favor the primary SS diagnosis with a TNF α mediated arthropathy. Arthropathy is a non-erosive intermittent polyarthritis with less synovial thickening and joint effusion than RA. On the other hand, however, because many patients with severe arthritis also meet the diagnostic criteria for RA, they are usually diagnosed with secondary RA [22].

Treatment

Once the diagnosis of primary SS has been made, physicians often find treating patients to be a challenge because of the wide spectrum of associated symptoms a patient may have. One study by Tomiita *et al.* [11], suggest that orally administered pilocarpine hydrochloride is a safe and effective way to treat the oral symptoms of both primary and secondary juvenile SS. The study demonstrated that saliva production in all participants increased, however the degree of improvement varied between individuals. The study proposes two mechanisms to explain these changes. The first is that because pilocarpine acts primarily as a muscarinic agonist, stimulating muscarinic receptors. Considering this mechanism, a salivary gland that has decreased function due to fewer functioning muscarinic receptors may show little increase in salivary production [2]. The other mechanism is proposed by Naito *et al.* [23], which states that some patients with SS have autoantibodies to muscarinic 3-acetylcholine -receptor (M3R), and this antibody is found in high prevalence in juvenile SS patients. However, anti-M3R antibody levels were not measured in this study. Therefore, additional studies are warranted to investigate the mechanism underlying pilocarpine treatment [2]. Furthermore, the patient with secondary SS had a better response to the pilocarpine treatment than the patients with primary SS. This may suggest that the mechanism of salivary gland destruction between primary and secondary SS patients is different; however there is not much evidence to support this idea. While the results of this study are promising, only 5 juvenile patients with SS were included in this study. Further studies with a larger patient pool are needed to confirm and support the evidence.

Conclusion

In conclusion, trends in manifestations, diagnostic markers and viable treatment methods are being discovered and hold promising results for juvenile patients affected by SS. However, because of the vast spectrum of manifestations and low prevalence of juvenile SS, it is difficult to conduct research studies with enough participants to yield evidence applicable to a large population. Further research is needed to help clinicians better understand, diagnose and treat patients with SS. Considering the low prevalence, it might be useful to do a multi-centric study to ensure that the patient pool is large enough so that a conclusion may be reached.

Acknowledgements

None

Conflict of interest and funding

No sources of funding were used in this literature review. There is no conflict of interest.

References

- Kobayashi I, Furuta H, Tame A, Kawamura N, Kojima K, et al. (1996) Complications of childhood Sjögren syndrome. *Eur J Pediatr* 155: 890-894. [Crossref]
- Tomiita M, Takei S, Kuwada N, Nonaka Y, Saito K, et al. (2010) Efficacy and safety of orally administered pilocarpine hydrochloride for patients with juvenile-onset Sjögren's syndrome. *Mod Rheumatol* 20: 486-490. [Crossref]
- Patel R, Shahane A (2014) The epidemiology of Sjögren's syndrome. *Clin Epidemiol* 6: 247-255. [Crossref]
- Sjögren's Syndrome Foundation (2014) What is Sjögren's? [Brochure].
- Movva Suneel, Carsons Steven (2014) Pediatric Allergy, Immunology, and Pulmonology. 27(3): 111-114.
- Baszisz K, Toib D, Cooper M, French A, White A (2012) Recurrent parotitis as a presentation of primary pediatric Sjögren syndrome. *Pediatrics* 129: 179-182. [Crossref]
- Singer N, Tomanova-Soltys I, Lowe R (2008) Sjögren's Syndrome in Childhood. *Pediatric Rheumatology* 10: 147-155.
- Longhi BS, Appenzeller S, Centeville M, Gusmão RJ, Marini R (2011) Primary Sjögren's syndrome in children: is a family approach indicated? *Clinics (Sao Paulo)* 66: 1991-1993. [Crossref]
- Alp H, Orbak Z, Erdogan T, Karabag K, Gursan N (2011) Recurrent parotitis as a first manifestation in a child with primary Sjögren's syndrome. *West Indian Med J* 60: 685-687. [Crossref]
- Mizuno Y, Hara T, Hatae K, Hirano T, Ueda K, et al. (1989) Recurrent parotid gland enlargement as an initial manifestation of Sjögren syndrome in children. *Eur J Pediatr* 148: 414-416. [Crossref]
- Tomiita M, Saito K, Kohno Y, Shimojo N, Fujikawa S, et al. (1997) The clinical features of Sjögren's syndrome in Japanese children. *Acta Paediatr Jpn* 39: 268-272. [Crossref]
- Kobayashi I, Kawamura N, Okano M, Shikano T, Mizumoto M, et al. (2001) Anti-alpha-fodrin autoantibody is an early diagnostic marker for childhood primary Sjögren's syndrome. *J Rheumatol* 28: 363-365. [Crossref]
- Maeno N, Takei S, Imanaka H, Oda H, Yanagi K, et al. (2001) Anti-alpha-fodrin antibodies in Sjögren's syndrome in children. *J Rheumatol* 28: 860-864. [Crossref]
- Houghton K, Malleson P, Cabral D, Petty R, Tucker L (2005) Primary Sjögren's syndrome in children and adolescents: are proposed diagnostic criteria applicable? *J Rheumatol* 32: 2225-2232. [Crossref]
- Siamopoulou-Mavridou A, Drosos AA, Andonopoulos AP (1989) Sjögren syndrome in childhood: report of two cases. *Eur J Pediatr* 148: 523-524. [Crossref]
- Ohtsuka T, Saito Y, Hasegawa M, Tatsuno M, Takita S, et al. (1995) Central nervous system disease in a child with primary Sjögren syndrome. *J Pediatr* 127: 961-963. [Crossref]
- Igarashi T, Itoh Y, Shimizu A, Igarashi T, Yoshizaki K, et al. (2012) A case of juvenile Sjögren's syndrome with interstitial nephritis. *J Nippon Med Sch* 79: 286-290. [Crossref]
- Bogdanović R, Basta-Jovanović G, Putnik J, Stajić N, Paripović A (2013) Renal involvement in primary Sjögren syndrome of childhood: case report and literature review. *Mod Rheumatol* 23: 182-189. [Crossref]
- Pessler F, Emery H, Dai L, Wu YM, Monash B, et al. (2006) The spectrum of renal tubular acidosis in paediatric Sjögren syndrome. *Rheumatology (Oxford)* 45: 85-91. [Crossref]
- Bartunkova J, Sediva A, Vencovsky J, Tesar V (1999) Primary Sjögren's syndrome in children and adolescents: proposal for diagnostic criteria. *Clin Exp Rheumatol* 17: 381-6. [Crossref]
- Shiari R, Kobayashi I, Toita N, Hatano N, Kawamura N, et al. (2006) Epitope mapping of Anti- α -fodrin autoantibody in juvenile Sjögren's syndrome: Difference in major epitopes between primary and secondary cases. *J Rheumatol* 33(7): 1395-1400. [Crossref]
- Pessler F, Monash B, Rettig P, Forbes B, Kreiger PA, et al. (2006) Sjögren syndrome in a child: favorable response of the arthritis to TNF α blockade. *Clin Rheumatol* 25: 746-748. [Crossref]
- Naito Y, Matsumoto I, Wakamatsu E, Goto D, Ito S, et al. (2006) Altered peptidyl ligands regulate muscarinic acetylcholine receptor reactive T cells of patients with Sjögren's syndrome. *Ann Rheum Dis* 65: 269-271. [Crossref]

Copyright: ©2017 Hasan I. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.