Audiological Profile in Primary Sjögren's Syndrome in a Tertiary Care Setting and its Clinical Implications

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Abstract This study aims to assess the frequency and the profile of hearing loss among patients with primary Sjögren's syndrome in a tertiary care hospital in India and to look for an association between hearing loss and immunological parameters (anti-SSA antibody, anti-SSB antibody, anticardiolipin antibodies, complements C3 and C4). This prospective observational study was done from January 2011 to October 2011 on consecutive patients diagnosed with primary Sjögren's syndrome in our tertiary care hospital. All patients underwent a puretone audiogram, tympanogram and acoustic reflex testing. The results of the tests were correlated with clinical and immunological findings. The frequency of audiometrically confirmed hearing loss in primary Sjögren's syndrome was estimated to be 78.38 %, though only 17.24 % complained of hearing loss; minimal to mild sensorineural hearing loss were the most common varieties. The commonest finding on tympanometry was 'A' type curve and acoustic reflex was absent in 18.92 % of cases. There was no association between hearing loss and age, sicca symptoms, systemic symptoms or immunological test results in primary Sjögren's syndrome. There was a high prevalence of hearing loss among patients with primary Sjögren's syndrome, but most patients were unaware of this. Hearing assessment and regular monitoring of hearing thresholds is advisable for all patients with primary Sjögren's syndrome.

Keywords Autoimmune disease · Sjögren's syndrome · Hearing loss · Autoimmune inner ear disease

Introduction

Sjögren's Syndrome (SS) is a systemic autoimmune disease mainly affecting the exocrine glands. The disease usually presents with persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands. It is diagnosed by validated classification criteria namely the American-European Consensus Group (AECG) [1] and the new American College of Rheumatology (ACR)/SICCA criteria [2]. When there is no other associated systemic autoimmune disease, this condition is termed as primary Sjögren's syndrome (pSS) [3]. The clinical spectrum of the disease may range from an apparent autoimmune exocrinopathy to an overt systemic process with multiple extraglandular manifestations [3]. Other exocrine glands including those in the pancreas, bronchial tree and gastrointestinal tract may also be affected. The spectrum of clinical manifestations of pSS is very wide, ranging from mucosal dryness to more systemic complaints affecting predominantly the musculoskeletal, pulmonary, renal, neurological and vascular systems. Peripheral nervous system disease manifests commonly as peripheral sensory neuropathy or more rarely as mononeuritis multiplex [4]. Of the 2–4 million people in the United States with pSS [5], 1 million have established diagnosis fulfilling stringent criteria. In India, pSS was previously thought to be rare, but recent data suggest otherwise [6]. The disease primarily affects women, with a very high female-male ratio of 9:1 [5] similar to several other systemic autoimmune rheumatologic diseases. This could be because of the influence of sex hormones, some

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unknown role of X chromosome related genes or other epigenetic factors influencing the homeostasis of women's health. pSS may occur in all ages [5], but majority seem to have the onset of disease between the fourth and sixth decades of life. In Indian patients, the disease seems to herald itself a decade earlier [6].

Approximately 60 % of SS patients have the disease secondary to an accompanying autoimmune disorder such as rheumatoid arthritis, systemic lupus erythematosus, or systemic sclerosis, collectively known as secondary Sjögren's syndrome (sSS) [5].

Autoimmune inner ear disease (AIED) was defined by McCabe as a rapidly progressive bilateral sensorineural hearing loss (SNHL) that responds to the administration of immunosuppressive agents [7]. It is known as primary AIED if the pathology is restricted to the ear, whereas a multi systemic, organ non specific auto immune disease involving the inner ear results in secondary AIED. The pathogenesis of immune-mediated sensorineural hearing loss is not clear. Immune complex mediated vasculitis in the inner ear [8] and auto antibodies directed against inner-ear antigenic epitopes [9] may be responsible. Although ear involvement is not uncommon in autoimmune diseases, data on this problem in pSS is scarce [10, 11]. SNHL has been commonly reported as the first otologic manifestation of some of the autoimmune diseases [8, 9, 12–14]. Studies have reported the prevalence of hearing loss in pSS to be in the range of 21–46 % [10, 15–17]. Anticardiolipin antibodies (ACA) may be associated with sudden SNHL in patients with autoimmune diseases. Tumiaty et al. [18] reported that ACA may be responsible for SNHL in pSS. Their study showed that 90 % of pSS had antibodies to SSA and 66 % had antibodies to SSB. All pSS patients with SNHL had antibodies to SSA. Sixty four percent of patients with SNHL had ACA as compared to 18 % in the normal hearing group [10]. While low C4 level is seen in vasculitis associated with pSS, it is unclear if that is helpful in monitoring hearing loss [19].

This study aims to determine the frequency and the profile of hearing loss among Asian Indian patients with pSS in a tertiary care teaching hospital in southern India; the secondary objective was to look for any association between hearing loss and immunological abnormalities namely positive anti-SSA antibody, anti-SSB antibody, ACA and low complements C3 and C4 status in these patients.

Patients and Methods

This prospective observational study was conducted over a period of 10 months (January 2011–October 2011) in the Clinical Immunology and Rheumatology clinic and the

Audio-Vestibular clinic of our tertiary care centre after obtaining approval from the Institutional review board and Ethics committee of our institution. Consecutive patients of pSS fulfilling the AECG criteria in the 20–60 year age group were recruited from Clinical Immunology and Rheumatology clinic [1]. Informed consent was obtained from all patients for participation in the study. Those with a past history of ear disease, known to cause permanent sensorineural or conductive hearing loss e.g. chronic suppurative otitis media, history of intake of ototoxic drugs like aminoglycosides and loop diuretics, history of head injury, ear trauma, ear surgery, otosclerosis or past history of exposure to sudden loud explosive noise were excluded.

Once enrolled in the study, a detailed history was taken based on a structured questionnaire and a complete ENT examination was performed. Patients then underwent pure tone audiometry and impedance audiometry. The pure tone audiogram was done using a calibrated GSI-61 clinical audiometer in an acoustically treated, sound-proof, two rooms setting. The modified Hughson-Westlake technique was used for estimating the thresholds [20]. The degree of hearing loss was determined using the pure tone average of thresholds at 3 frequencies 500 Hz, 1 and 2 kHz. Impedance audiometry included tympanometry and acoustic reflex testing which was performed using a calibrated GSI Tymptstar middle ear analyzer impedance audiometer. Blood investigations included complements C3 and C4, anti-SSA, anti-SSB antibody, Lupus anticoagulant and ACA. Commercial ELISA kits (Euroimmun, Lubeck, Germany) were used for detection of anti-SSA and anti-SSB antibodies and ACA. Serum complements C3 and C4 were estimated by nephelometry (Siemens Healthcare, Deerfield, USA) in the autoantibody lab. The normal range for anti-SSA was <20Ru/ml, anti-SSB: <20Ru/ml, ACA: <12units/ml, C3: 90–180 mg/dl and C4:10–40 mg/dl.

The data was analyzed using SPSS Version 11.0. Continuous variables and categorical variables were summarized using mean $\pm$ standard deviation and frequencies with percentages respectively. Association between hearing loss and other categorical variables were assessed using the Chi Square test.

Results

Clinical Profile

After applying the inclusion and exclusion criteria, 37 patients were recruited in the study. Of the total cohort, 18 patients belonged to the 20–45 years age group and the remaining 19 were in the 46–60 years age group. The mean age of the study group was 45.8 ± 10.2 years; the

cohort consisted of 36 females and a 37 years old male patient.

Of the 37 patients, 34 (91.89 %) had sicca symptoms in the form of dryness of eyes and mouth. The median duration of sicca symptoms was 24 months (range: 3–180 months). Three (8.1 %) patients complained of recurrent parotid swelling, while 18 (48.7 %) had history of multiple joint pain. Schirmer's test was done in 28 out of the 37 patients; it was not done in 9 patients, however they fulfilled criteria for the diagnosis of pSS even without this. Twenty seven out of these 28 (96.43 %) patients had a positive Schirmer's test confirming dry eyes. Of the 30 patients who underwent lip biopsy, 15 (50 %) had a grade 4, 14 (46.67 %) had grade 3 and 1 (3.33 %) had grade 1 inflammation. Again, the patient with grade 1 inflammation in lip biopsy did fulfill adequate criteria in spite of the negative histology. The sole male patient in our study had grade 4 inflammation. Seven patients (18.92 %) did not undergo lip biopsy as they were not willing for biopsy, yet they fulfilled adequate AECG classification criteria to be labeled as definite pSS. The results of the serological tests are shown in Table 1. Of the 34 patients who had complement assays done, only 1 patient (2.94 %) had a low C3 and C4 level.

Of the 37 patients, 17 (45.9 %) were on treatment with hydroxychloroquine (HCQ) alone, 1 (2.7 %) on methotrexate (MTX) alone and 17 (45.9 %) were on both HCQ and MTX. The median duration of HCQ treatment was 15 months (range: 2–84 months). The median duration of MTX treatment was 16 months (range: 3–60 months). Six (16.22 %) patients had hypertension, 8 (21.62 %) had hypothyroidism and 1 (2.7 %) had dyslipidemia. None were diabetic.

Audiological Profile

Table 2 lists audiovestibular symptoms of our patients with pSS. The five patients who complained of hearing loss did not have tinnitus and the 5 who complained of tinnitus did not have hearing loss. The mean thresholds at various frequencies are summarized in Table 3. The mean pure tone average (of thresholds at 500 Hz, 1 and 2 kHz) in the right ear was 18.1 ± 5.4 dB and in the left ear was 19.6 ± 9.5 dB.

Of the 37 patients, 29 (78.38 %) were found to have hearing loss on audiometry; the degree of hearing loss (based on the pure tone average) was minimal in 24 (64.85 %), mild in 4 (10.8 %) and moderate in 1 (2.7 %). Normal hearing on audiometry was documented only in 8 (21.62 %) patients. Among the 29 patients with audiometric hearing impairment, 28 had sensorineural and 1 had mixed hearing loss of moderate severity. Of these 29 patients, 24 (82.76 %) had bilateral and 5 (17.24 %) had

Table 1 Serological test results

Tests	Positive	Mean titre (SD)
Anti SS-A n = 35	23 (65.71 %)	98.8 (91.45) Ru/ml
Anti SS-B n = 35	12 (34.29 %)	68.51(107.6) Ru/ml
ACA n = 31	2 (6.45 %)	3.76 (5.79) units/ml

n denotes the number of patients in whom the tests were done

unilateral hearing loss. The only male patient in this study group had bilateral minimal SNHL.

Audiometric analysis further revealed hearing loss affecting higher frequencies namely 4 and 8 kHz in 27 out of these 29 patients. The mean value of the average threshold for the high frequencies (4 and 8 kHz) was 26.4 ± 12.1 dB with a maximum value of 82.5 dB.

Table 4 and Fig. 1 show the results of Impedance testing and acoustic reflex testing in the study group. The commonest type of tympanogram was 'A' type, which was found in 83.78 % of patients. Acoustic reflexes were absent in 18.9 % patients.

There were no differences in hearing loss between the age groups 20–45 and 46–60 years (*p* value = 0.935). There was no significant correlation between hearing loss and sicca symptoms, duration of sicca symptoms, presence of joint pain, treatment with HCQ or MTX, grade of lip biopsy, anti-SSA/anti-SSB antibody titers, anticardiolipin antibody titers and serum complement levels (Tables 5, 6).

Of the 29 patients with documented hearing loss, only 5 (17.24 %) patients subjectively complained of decreased hearing. Surprisingly, 24 (82.76 %) patients were not even aware that they had decreased hearing. All the 5 patients who complained of decreased hearing had a documented hearing loss.

Discussion

Our study recruited a larger sample size as compared to earlier studies with a similar research question from other countries [10, 17]. This sample size was feasible in view of the nature of our large tertiary care referral centre catering to the whole of the Indian subcontinent. The mean age of patients recruited in this study (45 years) was considerably lower than other studies (55 years), possibly due to the relatively younger demographic profile of our country [10]. In keeping with what is known in literature, all but one patient in this study were women.

Duration of illness is a reflection of access to specialist services. In this study, patients reported within a mean

Table 2 Audiovestibular symptoms* among 37 patients

Audiovestibular symptoms		Present (%)	Total (%)
Hearing loss	Unilateral	3 (8.1)	5 (13.5)
	Bilateral	2 (5.4)	
Tinnitus	Unilateral	4 (10.8)	5 (13.5)
	Bilateral	1 (2.7)	
Vertigo		3 (8.1)	3 (8.1)

* Each patient had one or more audiovestibular symptom

duration of 4.5 years since the onset of symptoms as compared to other studies reviewed namely 8.3 years by Ziavara et al. [17] and 3 years by Hatzopoulos et al. [16].

Hearing assessment in normal Indian adults (<60 years of age) with no risk factors for hearing loss show the prevalence of sensorineural hearing loss to range from 0 to 6 % [21, 22] and males comprising two-thirds of them [21]. The 78 % prevalence of hearing loss in pSS noted in our study with predominantly female population, therefore, does not reflect the commonly prevalent scenario of hearing impairment in the normal Indian population. A handful of other studies on hearing loss in pSS also report figures much higher than the Indian control population data; our figure of hearing loss in 78 % of pSS patients, however, is the highest as compared to the reports of 46 % by Tumiaty et al. [10], 21.4 % by Trott et al. [15], 36.3 % by Hatzopoulos et al. [16] and 22.5 % by Ziavara et al. [17]. SNHL was the commonest hearing loss in our study (97 %) and this is similar to other studies reviewed from published literature [10, 16, 17]. Doig et al.'s study [23] is the only study reporting conductive hearing loss in their patients (5

Fig. 1 Acoustic reflexes in 37 patients with pSS

out of 22 pSS patients with hearing loss). Authors in that study suggested dryness of the mucous membranes of the eustachian tube and middle ear as the cause of conductive hearing loss in pSS.

There was a predominance of bilateral hearing loss (82.8 %) in our study similar to the findings in Tumiaty's study (71.43 %) [10]. Ziavara et al. [17] found bilateral hearing loss in 44 % and unilateral hearing loss in 56 % of their patients with pSS. The predominantly bilateral involvement found in our study may suggest the systemic nature of the underlying pathology, which is often the rule in autoimmune diseases like pSS [7].

There is a difference in the severity of SNHL between this study and published literature. Of 29 with hearing loss in this study, all but one patient had only minimal to mild SNHL, classified on the basis of average pure tone

Table 3 Mean and standard deviation of puretone thresholds at various frequencies

Frequency	Right		Left	
	Air conduction (SD)	Bone conduction (SD)	Air conduction (SD)	Bone conduction (SD)
250 Hz	18.6 (6.0)	16.6 (5.0)	20.6 (10.7)	17.2 (6.5)
500 Hz	17.7 (5.5)	15.9 (5.0)	20.5 (10.6)	17.1 (5.4)
1 kHz	17.7 (5.1)	17.2 (4.8)	18.5 (9.0)	16.4 (5.4)
2 kHz	18.8 (8.2)	18.4 (7.3)	20.3 (10.1)	19.1 (7.0)
4 kHz	23.6 (10.6)	21.9 (8.8)	22.8 (13.8)	20.5 (9.2)
8 kHz	29.5 (18.5)	–	28.4 (15.1)	–

Table 4 Tympanometry results in 37 patients

Side	A n (%)	As n (%)	Ad n (%)	B n (%)	C n (%)
Right	31 (83.78 %)	2 (5.4 %)	3 (8.11 %)	0	1 (2.7 %)
Left	31 (83.78 %)	3 (8.11 %)	0	2 (5.4 %)	1 (2.7 %)

Table 5 Correlation between hearing loss and various clinical parameters

		Hearing loss		<i>p</i> value
		Yes	No	
Sicca symptoms	Yes	27	7	0.607
	No	2	1	
Joint pain	Yes	12	6	0.092
	No	17	2	
On treatment with HCQ	Yes	27	7	0.607
	No	2	1	
On treatment with MTX	Yes	12	6	0.092
	No	17	2	
Lip biopsy grade	1	1	0	0.186
	3	13	1	
	4	10	5	
Anti-SSA antibody	Positive	19	4	0.593
	Negative	9	3	
Anti-SSB antibody	Positive	9	3	0.827
	Negative	18	5	
Anticardiolipin antibody	Positive	1	1	0.591
	Negative	23	6	
C3 levels	Low	1	0	0.539
	Normal	25	8	
C4 levels	Low	1	0	0.706
	Normal	23	7	
	Elevated	2	1	

threshold for the speech frequencies 500, 1000, and 2000 Hz. Tumati et al. [10] studied 15 pSS patients with hearing loss, of whom 9 had minimal hearing loss, 1 had mild hearing loss, 4 had moderate hearing loss and 1 had severe hearing loss. In accordance with earlier studies [10, 17, 24], our study also showed hearing loss in pSS mainly affects the higher frequencies.

We found no association between documented hearing loss and age as seen in previous studies [10, 16]. This could also be because our cohort consisted of younger patients. Ziavara et al. [17] noted association between SNHL and disease duration. Tumati et al. [10] and Hatzopoulos [16]

however, did not find any such association between disease duration and abnormal hearing in pSS. When we assessed the presence of hearing loss in 3 subsets, namely those with duration of disease of <1 year, 1–5 years and >5 years, we noted a decreasing trend in occurrence of hearing loss with increasing duration of disease; this difference was, however, not significant (*p* value = 0.660). A larger sample size may clarify this observation.

The commonest type of tympanogram observed in our study was A type (83.78 %). In contrast to the data reported by Hatzopoulos [16], who found that all their 22 patients with pSS had a normal tympanogram, a small proportion (16.22 %) of patients in our study had As, Ad, B and C types of curves also. Reflexes were absent in seven patients (18.9 %) in contrast to Hatzopoulos's cohort, where all patients had preserved reflexes. Tumati et al. [10] found middle-ear pressure to be normal in all their patients and there were no significant differences in mean compliance value between controls and the patients with SS.

Only 5 (17.24 %) patients amongst the 29 with documented hearing loss in our study, complained of a decreased hearing; 24 (82.76 %) did not complain of decreased hearing. Tumati et al. [10] found that 9 of 14 (64.28 %) with hearing loss were asymptomatic and hearing loss was detectable only on audiometry in them. Diog et al. [23] found none complaining of decreased hearing among 27 % of their patients with audiometrically documented hearing loss. In our study, a higher proportion of asymptomatic hearing loss was noted as compared to Tumati et al. [10]. Hearing loss may be the first audiological manifestation of pSS [16]. The detection of SNHL in these patients again points to the probability of a systemic pathology, possibly autoimmune involvement of the ear in this multisystemic autoimmune disease. It is therefore important to note that hearing evaluation should be made a part of the routine work up of pSS patients.

Duration of treatment with HCQ or MTX did not significantly alter the proportion of patients with hearing loss. This may suggest that these drugs have little adverse effect on hearing in patient with pSS.

Table 6 Correlation between duration of sicca symptoms and hearing loss

Parameter		Duration			Chi square value	<i>p</i> value
		<1 year	1–5 years	>5 years		
Dry eye	Hearing loss	11	11	5	2.62	0.27
	Normal	2	5	0		
Dry mouth	Hearing loss	9	13	5	1.90	0.39
	Normal	2	5	0		

Tumiati et al. [10] has reported a correlation between SNHL and anti-SSA and ACA titres in SS. However similar to the study by Ziavara et al. [17], our study found no such correlation between hearing loss and the presence of auto-antibodies.

The pathogenesis of immune-mediated SNHL is still not clear. This is a preliminary analysis to find the audiological profile of patients with pSS. Further studies with larger sample size are necessary to establish the probable etiologies in this relatively common autoimmune multi-systemic condition.

Limitations of the Study

Recruitment of age and sex matched controls for comparison of hearing thresholds would have further helped in the interpretation of the results of this study.

Audiological evaluation in pSS patients prior to starting treatment would have provided more information on the disease process without modification by medications. This is however not possible in a tertiary care situation, as patients have already been under treatment from other centers for years before being referred here.

Further audiological evaluation for identifying the site of pathology on the patients detected to have hearing loss could not be done due to several logistic issues. Such an evaluation would have been helpful in suggesting the anatomical and etiopathological nature of the hearing impairment.

It would have been useful to do serial audiological tests to see the progression of hearing loss over time in the same patient. That would provide a greater insight into the natural history of hearing loss in pSS.

Conclusions

The frequency of audiometrically confirmed hearing loss in pSS was estimated to be 78.38 % in this study, the commonest type of hearing loss being minimal to mild sensorineural hearing loss. Mostly, hearing loss was subclinical as a majority were unaware of their hearing impairment. The higher frequencies were more affected than lower frequencies in our cohort. The commonest tympanometry finding was an 'A' type curve and acoustic reflex was absent in 18.92 %. The frequency of hearing loss was found to be numerically higher in the first year of onset of pSS rather than after 5 years of disease duration. There seems to be no correlation between hearing loss and age, sicca symptoms, systemic symptoms and immunological test results in pSS. It would be advisable to include

assessment and regular monitoring of hearing thresholds in patients diagnosed with pSS.

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Compliance with Ethical Standards

Conflict of interest C. V. Thanooja, Ann Mary Augustine, Anjali Lepcha, Pulukool Sandhya, Amit Kumar Tyagi, Debashish Danda, Achamma Balraj declare that they have no conflict of interest.

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Ethical Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional review board and ethics committee and with the 1964 Helsinki declaration and its later amendments.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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