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EPIDEMIOLOGY AND DIAGNOSTICS OF PRIMARY SJÖGREN'S SYNDROME EPIDEMIOLOGIJA I DIJAGNOSTIKA PRIMARNOGA SJÖGRENOVOG SINDROMA

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Summary

This review paper contains selected aspects of Sjögren's syndrome. It consists of epidemiology, ultrasound of salivary glands and antimuscarinic antibodies. The first part present studies aimed to determine the prevalence and the incidence of the disease with special

emphasize on epidemiological studies performed in Slovenia. This is followed by the demonstration of the role of ultrasound of salivary glands in the diagnosis of Sjögren's syndrome and the value of antimuscarinic antibodies in global assesment of the secretory failure.

Key words

Sjögren's syndrome, epidemiology, ultrasound, antimuscarinic antibodies

Sažetak

U preglednom su članku opisani epidemiologija, ultrazvučni nalaz slinovnica i antimuskarinska antitijela u Sjögrenovom sindromu. U prvomu su dijelu rada prikazani prevalencija i incidencija bolesti u odnosu na epi-

demiološke studije u Sloveniji. Prikazana je uloga ultrazvučne pretrage slinovnica u dijagnozi Sjögrenova sindroma i vrijednost antimuskarinskih antitijela u općoj procjeni sekrecijske poremtnje.

Ključne riječi

Sjögrenov sindrom, epidemiologija, ultrazvuk slinovnica, antimuskarinska antitijela

Introduction

Primary Sjögren's syndrome (pSS) is quite common systemic autoimmune disease. The ethiology is unknown and the pathogenesis still not completely understood. In the majority of cases it is not a life-threatening condition. However, sicca symptoms and fatigue can be very unpleasant and disabling. There are several problems in managing the disease. Often the diagnosis is late because of insufficient knowledge, atypical cases and rather complex diagnostic pro-

cedures. Additionally, the lack of effective treatment represent a major disadvantage in managing the disease.

We will focus on two important aspects of pSS: the epidemiology of pSS, and the diagnostic criteria and new possibilities in the assesment of Sjögren syndrome (SS). These assesments are still a matter of debate due to lack of accurate imaging procedures and recent knowledge about new possibly pathogenic autoantibodies.

Epidemiology

The prevalence of pSS is uncertain and the incidence has been studied only by two groups. The major problems derive from the diagnostic criteria. So far, nine different criteria has been published with substantionally different approaches resulting in the power of diagnosing pSS.

Prevalence of pSS

The disease primarily affects women during the fourth and fifth decade of life and has a female:male ratio of 9:1. Studies on geriatric populations have shown

a prevalence of pSS of 1,9-4,8% (1-3). The estimated prevalence of pSS in the general population in Slovenia is 0,6% according to the European criteria (4,5) and 0,3% according to the American-European criteria (6). The quoted prevalence is supported by studies performed by Dafni et al, Bjerrum and recently also by Bowman et al (7,8,9).

In our study 332 (183 females, 149 males) of the 889 invited individuals (37%) agreed to participate in

the study. After the first visit, 244 participants (73,5%) proved to be negative for three out of the six criteria, and were therefore eliminated from further tests. The remaining 88 participants were consecutively subjected to Rose Bengal score, salivary scintigraphy and minor salivary gland biopsy. Fifteen participants refused to perform either one or more of the proposed tests at the second study stage. Two women (0,6% of the 332 participants) both aged in their sixties, satisfied four of the six criteria for the classification of definite Sjögren's syndrome. An additional 53-yr-old men and the woman aged 40 also fulfilled four of the six criteria, but met the exclusion criteria (antihypertonic or neuroleptic therapy). We considered this estimated prevalence to be reliable despite three potential biases: (I) relatively high proportion of non-responders; (II) not identical age distribution of the study and region populations; (III) not all suspected participants agreed to undergo all the diagnostic tests at the second study stage. Considering the last bias the prevalence of pSS could be slightly underestimated.

Incidence of pSS

There have been only two published studies for the incidence of pSS, one from Olmsted County, Minnesota with 3,9 cases per 100000 population (10) and one from our group with the same incidence (11).

We prospectively examined all patients admitted to our Department of Rheumatology or referred to our outpatient clinic from 1 January 2000 to 31 December 2002 mainly due to sicca symptoms. Additionally, all patients initially referred to our department under other suspected diagnoses, but indicated by our rheumatologists for SS diagnostic tests based on medical history, clinical examination and/or serologic tests, were included during the above stated period, giving the final number of 248 patients. There is no other rheumatological department or outpatient clinic in the Ljubljana region with a Caucasian population of 599895. All patients were evaluated using the validated European criteria for SS.

After the first visit, all patients were asked to come to our department between 9 and 11 a.m., fasting and with no brushing of the teeth, mouth rinsing or tobacco smoking for at least 1 h before the examination. Six questions to assess both ocular and oral involvement were given to each patient. Information on co-morbidities, tobacco smo-

king and related treatment was collected at the same time. Besides the questionnaire, all patients were subjected to a Schirmer-I test, unstimulated salivary flow test, Rose Bengal score determination, as well as serological tests. If necessary, salivary scintigraphy and histopathological investigation of the minor salivary glands were carried out until 3 of the 6 European classification criteria for SS were shown to be negative or until SS was diagnosed. Table shows the clinical and laboratory data of the patients included in our study.

In general, there are two major problems in estimating the incidence of pSS. The first is that patients often delay seeking medical help for substantial periods of time after the onset of symptoms. Individuals with mild disease may not have sought medical attention, or the diagnosis may not have been suspected or established even if they were seen by a physician.

The second problem concerns the case definition of SS. SS in particular is a disease for which different diagnostic criteria have been proposed. Consequently, studies using differing diagnostic measures are not easily comparable (12).

Our study could have been enriched by recruiting patients of otorynolaryngologists, dentists and oral surgeons, but we believe that patient enrolment was close to optimum, based on the organization of the health system in Slovenia: there is no-cost access to general practitioners and specialists, the referral rate to specialists is very high, and it is highly unlikely that any patient would seek medical help for possible SS in another Slovenian region or abroad.

It is possible that some pSS patients were missed due to smoking that may have lowered focus scores and negatively influenced determination of anti-Ro and anti-La antibodies (13).

Table. The incidence of pSS - the presence of clinical, laboratory and other characteristics of SS in patients diagnosed with pSS and those not fulfilling the validated European classification criteria for SS
 Tablica. Incidencija pSS - prisutnost kliničkih, laboratorijskih i drugih karakteristika SS u bolesnika s dijagnozom pSS i onih koji ne zadovoljavaju Evropske klasifikacijske kriterije za SS

	Patients with pSS N=71		Patients not diagnosed w. pSS N=177	
	N (%)	ND (%)	N (%)	ND (%)
Ocular symptoms	64 (90,1)	0	133 (75,1)	0
Oral symptoms	62 (87,3)	0	128 (72,3)	0
Schirmer-I test*	20 (28,2)	0	30 (16,9)	0
Rose Bengal score	55 (78,6)	1 (1,4)	60 (34,3)	2 (1,1)
USF*	29 (41,4)	1 (1,4)	65 (37,1)	2 (1,1)
Salivary scintigraphy	55 (88,7)	9 (12,7)	53 (43,8)	56 (31,6)
Histopatology	39 (59,1)	5 (7,0)	3 (2,9)	73 (41,2)
ANA	58 (81,7)	0	72 (40,9)	1 (0,6)
Anti-Ro	36 (50,7)	0	7 (4,0)	1 (0,6)
Anti-La	16 (22,5)	0	1 (0,6)	1 (0,6)

ANA - antinuclear antibodies USF - unstimulated salivary flow test ND - not done

* The results were considered positive only in patients younger than 60 years

Diagnosics

Criteria for the diagnosis of SS mostly used in Europe consists of 6 items (ocular symptoms, oral symptoms, ocular signs, histopathology, salivary gland involvement and autoantibodies). Salivary gland involvement is suggested to be defined by a positive result in at least one of the following three diagnostic tests: salivary scintigraphy, parotid sialography, unstimulated salivary flow. Recently, other imaging modalities became of great interest including ultrasound (US) of salivary glands.

The presence of anti-Ro and anti-La antibodies represent one of the most important objective tests for the diagnosis of SS. Impaired salivation and tear formation can result from cholinergic dysfunction which can be mediated by anti-muscarinic autoantibodies, so far not studied extensively.

Ultrasound of salivary glands

Until now, only few attempts have been made to reveal the role of US of salivary glands in the diagnosis of SS (14,15,16,17). The authors used different diagnostic criteria which made the comparison of the results difficult.

We studied 218 consecutive patients with suspicious pSS due to sicca symptoms and other important clinical signs or laboratory results, US of both parotid and submandibular salivary glands was performed. US was carried out on ATL US machine with 5 to 12 MHz linear transducer. At the ultrasonographic examination we evaluated five parameters: the echogeneity, the inhomogeneity, the number of hypoechogenic areals, the hyperechogenic reflection and the clearness of salivary gland bor-

ders. pSS was established in 68 patients, the remaining 150 studied subjects, in whom pSS was not confirmed, represented the control group. All five US parameters were significantly associated with pSS. US score was calculated by summing up the five grades for structural changes determined in each of all four glands and ranked from 0 to 48. Setting the cut off for US score at 17, resulted in the best specificity (58,8%) to sensitivity (98,7%) ratio. With this approach we could reveal that 40/68 (58,8%) of pSS patients had US changes typical for SS (18,19).

Anti-muscarinic antibodies

A number of data supports the pathophysiological role of the circulating anti-muscarinic antibodies. The second extracellular loop domain of M3 muscarinic acetylcholine receptor (M3R) has been regarded as the ligand binding site (20).

We used the 25-mer synthetic peptide (KRTVPPG ECFIQFLSEFTITFGTAI) synthesized by Diagen, Ljubljana, Slovenia as the antigen for the detection of anti-M3R synthetic peptide antibodies. A reproducible ELISA with the cut off value, estimated at the 95 percentile of the controls (5/145 pos) was developed. Positive values for anti-M3R were measured in 16/95 pSS and secondary SS patients and 8/92 patients with systemic lupus erythematosus (SLE).

Statistically significant higher prevalence of anti-M3R were found in patients with pSS and secondary SS compared to patients with SLE ($p=0,047$) and healthy controls ($p=0,0012$). There was no significant difference between SLE patients and controls (21).

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