ORIGINAL STUDIES

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HYPOSALIVATION AS CLINICAL MARKER AND AGGRAVATOR OF COURSE OF REHUMATOID ARTHRITIS COMPLICATED WITH ESOPHAGUS LESION

The article handles the features of salivatory disorders in patients with rheumatoid arthritis (RA), their role in pathogenesis of esophageal complications. 149 RA patients were examined 99 of which had complications from the side of esophagus. In all cases esophagus pathology was diagnosed not earlier than 1 year after the RA diagnosis had been established. Statistical processing of the examination results showed positive associative relationship between presence of the esophageal complications, on the one hand, and sensation of dryness in mouth, presence on incomplete teeth row, manifestations of glossitis/stomatitis, on the other. The relationship was found between hyposalivation intensity and presence of esophagus lesions in RA patients. The decrease of quantity of functionally active minor salivary glands in RA patients was detected in case esophageal complications are present, compared to RA patients without esophagus pathology. It is shown that salivation rate and number of functionally active minor salivary glands reduce when RA activity increases. The conclusion is drawn that hyposalivation in patients with RA complicated by esophagus pathology is a factor which aggravates the course of the rheumatic disease, participates in forming the extraarticular RA manifestations and reflects the activity of the pathological process.

Keywords: *rheumatoid arthritis, hyposalivation, salivary glands, esophagus pathology, extraarticular manifestations, pathogenesis*

INTRODUCTION

The modern definitive models in definition of rheumatoid arthritis (RA) interpret it as a multi vector general pathologic immune-inflammatory disease which affects not only joints but also other organs and systems of patient. In certain cases clinical manifestations of the disease are confined to articular pathology proper, and in the other, pathological state, either from the very onset or as it progresses, acquires features of systemic disease with poly-organ affection (Folomeyeva O.M., 2008). RA extraarticular manifestations present though expected but practically uncontrollable attributive sign of this disease. On this background RA *visceralization* process should a priori be regarded as a factor which reflects aggravated course of the disease, deteriorates prognosis and requires correction in treatment and diagnostics.

Hyposalivation and its clinical manifestation xerostomia is one of the most frequent symptoms in the clinic of internal diseases. This pathologic state is registered in 80% of patients with insulin-dependent sugar diabetes (Ivanovski K. et al., 2012), in 17 to 50% of patients with arterial hypertension (Kumar P. et al., 2012; Nonzee V. et al., 2012), in case of iron-deficit anemia and tireotoxicosis (Baranovsky A.L., 2002). Conducive to the rise of hyposalivation is reception of medications such as amitriptyline, antihistaminic, antipsychotic, hypotensive (diuretic, calcium channel blockers, methyldopa) anticholinergic medications. Xerostomia is the pathologic state which depends on age: its prevalence among persons under 50 is 6% and goes up to 15% at the age of 65 (Orellana M.F. et al., 2006). But the highest expressiveness is acquired by this symptom in case of rheumatologic pathology. Dryness in mouth disturbs 100% of patients with Sjogren disease, 71.2% - with

systemic scleroderma (Kodak S. et al., 2013), 65% - with RA (Jensen J.L. et al., 1997).

Hyposalivation causes diseases of mouth cavity organs, teeth. However, next to the stomatology group of diseases, the target organ in case of xerostomia is esophagus. In multi vector pathogenesis of gastroesophageal reflux the hyposalivation takes one of the leading roles. In the system of esophagoprotection, due to physiological clearance of saliva, esophagus is *rinsed* and its peristaltic is initiated. Total volume of saliva, organic and inorganic compounds of this biological liquid provide pre-epithelial protection of esophagus. It is no wonder that 57.5% of patients with gastroesophageal reflux disease complain of sensation of dryness in mouth (Campisi G. et al., 2008). Next to this, in 67% of patients with Sjogren syndrome, the disease with absolute expressiveness of hyposalivation, gastroesophageal reflux is detected (Volter F., et al., 2004).

The purpose of the study is to assess the state of salivation and to identify the role of salivation disorders in genesis of esophageal complications in RA patients, find relationship between hyposalivation intensity and features of course of RA complicated by esophagus lesion.

SUBJECTS AND METHODS OF STUDY

149 RA patients were examined 99 out of which had esophageal complications (main group), and in 50 patients no signs of esophagus pathology were detected (reference group). The main group patients were aged 49.0+/-1.19 years, the reference group – 49.4+/-1.44 years. Among the members of the main group 82 (82.8%) were women and 17 (17.2%) – men; in the reference group – 42 (84%) and 8 (16%) respectively. RA anamnesis in the main group was 8.7+/-0.36 years, in the reference group – 8.1+/-0.37 years. In the main group rheumatoid factor was detected in 77.8% of patients, in the reference group – in 78.0%.

RA diagnostics was made in accordance with the Ukrainian Healthcare Ministry Order No.676 dated 12.10.2006 *Clinical Protocol of Medical Aid to Patients with Rheumatoid Arthritis.* Lesion of esophagus was diagnosed on the basis of typical symptoms and/or instrumental data. In all cases esophagus lesion was diagnosed not earlier than 1 year after RA diagnosis had been established.

The state of basal salivation was examined in the patients early in the morning on an empty stomach. The examined patient in sitting position swallowed the saliva which was present and for 10 min. after he/she was gathering the saliva which was passively secreting. The state of stimulated salivation was investigated using mechanical stimulation by chewing paraffin for 2 min. The number of functioning minor salivary glands (MSG) was counted using coloring with 1% water solution of methylene blue. 20 min. before counting salivation was stimulated by pilocarpine. The functioning MSGs were counted within 2x2 cm frame put on the surface of mucous membrane of lower lip. Tumor necrosis factor (TNF)-α concentration in serum was determined by enzyme immunoassay. The obtained results were compared with the examination results in 20 practically healthy persons (control group) aged 40 to 55.

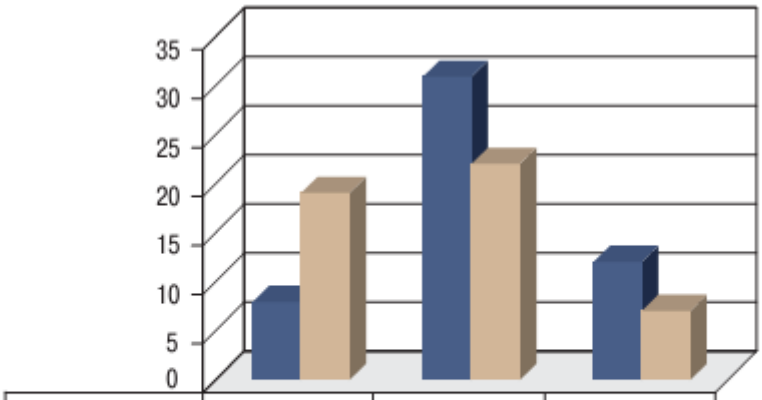
Statistical processing of the study results was made using methods of parametric statistics with calculation of mean arithmetic value (M) and mean square error (m). Reliability of differences was assessed using Student's criterion, critical level of significance in verification of statistical hypotheses was 0.05. Further, x^2 criterion, φ criterion – Fisher angular conversion were calculated, correlations were studied

(correlation coefficient – r), method of associative analysis was used with calculation of Jule's index – Q.

RESULTS AND DISCUSSION

When describing the results of the total questioning of the examined patients it should be noted that usually the complaints of dryness in mouth were not dominant. It may be attributed to the fact that the patients focused their attention on articular syndrome and did not attach much importance to other sensations. Meanwhile the deeper questioning detected such complaints in 51 (51.5%) out of 99 RA patients of the main group and in 16 (32%) out of 50 patients of the reference group. Differences in expressiveness of xerotomia between the patient groups were reliable: for RA (df=1, x^2=5.113; p=0.024; φ=2.294, significance zone at p<0.05->1.64). As a rule xerotomia was intermittent and troubled the examined persons in case of anxiety, unfavorable weather conditions (hot, frosty, windy weather), physical load, long conversation etc. Characteristic complaint of the patients was the need to take liquid when eating.

Assessment of dependence of dryness sensation in mouth on RA activity rate showed that most often this symptom was detected among the patients with III activity rate RA – in 12 (63.2%) out of 19 persons, and II activity rate – in 31 (58.5%) out of 53 patients; more seldom – in case of I activity rate RA – in 8 (29.6%) out of 27 patients. Statistical analysis of expression of the above-mentioned symptom showed direct relationship between symptom frequency and immune-inflammatory process activity rate (x^2=7.241; p=0.0268). Frequency distribution for this symptom as a function RA activity rate is given in fig.1.



Ступінь активності	I	II	III
Сухість – так, n	8	31	12
Сухість – ні, n	19	22	7

Fig.1. Distribution of frequency of dryness-in-mouth symptom manifestation in RA patients of the main group against RA activity rate.

In the figure:

Ступінь активності: activity rate

Сухість: dryness

Так: yes

Ні: no

According to examination of mouth cavity 96 (97%) out of 99 RA patients of the main group had incomplete teeth row, in the reference group the same index was 84% - 42 out of 50 patients. The signs of glossitis and/or stomatitis were registered in 75 (76%) patients of the main group and in 18 (36%) of the reference group. In RA patients the direct associative relationship is found between presence of esophageal complications on the one hand and sensation of dryness in mouth (Q=0.386), presence of incomplete teeth row (Q=0.718), manifestations of glossitis/stomatitis (Q=0.695) on the other.

Assessment of salivation state showed that the rate of basal and stimulated salivation in RA patients was lower than that in persons of the control group. It should be noted that it never occurred that in the examined persons the reduction of stimulated saliva secretion reached the level characteristic for Sjogren syndrome – 0.1 ml/min. In patients of the main group the examined sialometric indexes were lower than those in patients of the reference group (table 1). This fact showed that esophageal complications in RA patients occur with underlying more pronounced hyposalivatory state.

Table 1

Salivation State of Examined Persons, ml/min (M+/-m)

Salivation, ml/min.	**Group of examined persons and number of patients**		
	Main group (n=99)	**Reference group (n=50)**	**Control group (n=20)**
Basal	0.24+/-0.006***	0.30+/-0.007***	0.38+/-0.015
Stimulated	1.70+/-0.033###	1.98+/-0.046###	3.01+/-0.217

In tables 1 and 2 the differences are reliable if compared to the similar indexes of the persons of: *control group (t=9.580; p<0.001); **reference group (t=6.03; p<0.001); ***control group (t=5.484; p<0.001); #control group (t=11.740; p<0.001); ##reference group (t=4.792; p<0.001); ###control group (t=7.417; p<0.001).

During assessment of salivatory function disturbances, depending on immune-inflammatory process activity, in RA patients of the main group reduced salivation rate was detected with increasing RA activity (table 2). Such results reflected immune-inflammatory genesis of salivatory dysfunction in the examined patients. In favor of this thesis was also moderate negative correlation between content of TNF-α (superpowerful pro-inflammatory cytokine which reflects immune-inflammatory process activity) and the rate of basal (r=-0.41) and stimulated (r=-0.36) salivation.

Table 2

Salivation state and content of TNF-α in serum of RA patients of main group against activity of main disease (M+/-m)

Index	**RA activity rates and number of patients**		
	I (n=27)	**II (n=53**	**III (n=19)**
Salivation, ml/min.			
• Basal	0.28±0.010***	0.24±0.007***	0.20±0.011
• Stimulated	1.80±0.063#	1.69±0.044	1.59±0.074
TNF-α content ng/l	86.0±2.10§§§	92.9±1.79§§§	101.7±2.55

The number of functioning MSGs was determined in 72 RA patients of the main group amd in 41 RA patients of the reference group. The count results show that number of active glands in patients of the main group (17.7±0.22 MSGs) was smaller (t=2.622; p=0.010) than that in the patients of the reference group (18.0±0.28 MSGs) and the persons of the control group (19.0±0.49 MSGs; t=3.841; p<0.001).

In the main group of RA patients relationship between MSG number change and RA activity rate was investigated (fig.2).

The reliable differences were detected between number of MSG in RA patients of the main group with I activity rate and III activity rate (t=2.658; p=0.01). Number reduction of functionally active MSG, when rheumatic disease activity increases, shows the importance of inflammatory process in bringing about such pathologic state. Local mechanism of MSG inactivation is focal sialadenitis present in 80% of RA patients (Helenius L.M.J. et al., 2001).

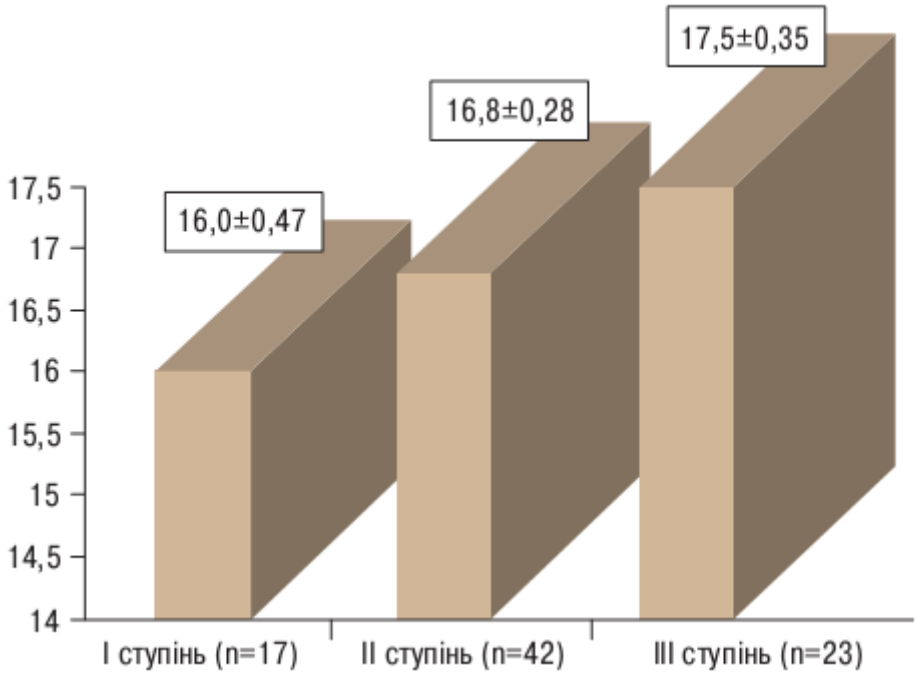


Fig.2. Number of MSGs in RA patients of the main group against RA activity rate (M±m)

Presence of salivatory disorders in case of RA should be taken into consideration in the clinical practice. Manifestations of hyposalivation (stomatitis, glossitis) may restrict administration of certain medications of RA basic therapy such as methotrexate, sulfasalazine, gold medications, azathioprine for which lesion of mouth cavity is one of side effects (Svintsitsky A.S. et al., 2006; Kovalenko V.N., Vikniriv A.P. (ed.), 2009). Therefore incomplete basic therapy of rheumatologic pathology won't produce expected disease-modifying effect. Besides, insufficient quality of food mechanical processing due to lack of teeth with underlying hyposalivation will conduce to contact damage of upper sections of nutritional tract (mouth cavity, esophagus) and give rise to additional extraarticular manifestations of the main disease.

CONCLUSIONS

Salivatory disorders in RA patients occur in the form of hyposalivation which has generalized nature: the rate reduces both of basal and stimulated phase of this process, number of functionally active MSGs decreases. Acting as an extraarticular RA manifestation, the salivatory disorders conduce to rise of esophageal lesions i.e. act as an aggravator in pathogenesis of *visceralization* of main disease. Next to this, hyposalivation expressiveness in RA patients with esophageal complications rises as the main disease activity increases. Therefore hyposalivation to a certain extent may be regarded as a clinical marker of aggressive course of RA complicated by lesion of esophagus.

BIBLIOGRAPHY

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