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SELF-ASSESSED QUALITY OF LIFE (QOL) OF RESIDENTS RECEIVING LEVEL 2 AND LEVEL 3 SOCIAL SERVICES IN COUNTY-OWNED NURSING HOMES IN THE CITY OF ZAGREB

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The aim was to analyze whether there is significant difference in self-assessment of the examined domains of the quality of life in residents receiving level 2 and level 3 social services in county-owned nursing homes in the City of Zagreb. This analytical cross-sectional survey was conducted successively (2018-2019) in 3 county-owned nursing homes in Zagreb including residents from nursing homes with levels 2 and 3 social services. The Quality of Life Scales for Nursing Home Residents 2001 test was used to examine the self-assessed quality of life in 92 residents aged ≥65, while Barthel Index modified by Shah, Vanclay and Cooper (MBI) was used to assess their functional independence. General sociodemographic variables were used including the level of social services provided. Study results showed that the self-assessed domains of functional competence (Z=5.050), privacy (Z=4.687), meaningful activity (Z=4.632), interpersonal relationships (Z=3.394), autonomy (Z=3.352) and individuality (Z=3.755) (p<0.001 all) were significantly higher among residents receiving level 2 versus level 3 social services. Self-assessed quality of life (N=92) showed the lowest level in the domain of food enjoyment (Me=11.40; IQR=9.02-11.40). In conclusion, difference in the examined domains of self-assessed quality of life between level 2 and level 3 users of social services in nursing homes guides the gerontologic multidisciplinary team in selecting interventions that can contribute to improving the quality of life of the elderly, especially the functionally dependent ones who need help of others in all areas of functioning (level 3 social services). The self-assessed quality of life of residents receiving level 2 and level 3 social services showed the lowest level in the domain of food enjoyment, which indicates the need for interventions in the implementation gerontologic nutritional standards and menus in nursing homes.

Key words: functional independence, nursing homes, quality of life self-assessment, the elderly

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INTRODUCTION

There are numerous specific qualities in the elderly population, which undoubtedly affect the self-assessment of their quality of life (QOL) (1). Resources provided by society for the elderly who are functionally disabled or who are unable to live independently (2), namely home care and residential care, are particularly important. Loss of functional independence is a factor associated with greater dependency of the elderly on help from others and on health care (3), and is one of the main reasons for leaving their homes (4,5). The inability of the elderly to perform basic activities of daily living (ADL) in their home is a significant predictor of their dependence on someone else's care, placement in the nursing home, and death (6,7).

Changes resulting from moving into a nursing home are noticed in social interactions and adaptation to domains that include privacy, dignity and independence (8). Satisfaction with the examined domains of elderly people's quality of life is connected with age, gender, number of health problems, and level of functional independence (9-11). Personal perception of the QOL

of the elderly is also influenced by cultural context, personal goals, social network, interpersonal relationships (12-14), and many other factors.

The phenomenon of aging is undoubtedly connected to the QOL of the elderly individual, and research indicates the importance of age structure factors or gender differentiation as, for example, in nursing homes, men and younger old people often report better health and quality of life (15). Likewise, the results of some studies showed positive correlation between QOL and increasing age, and older age was associated with better self-assessment of QOL in elderly day care centre (16). Research indicates that lower levels of functional independence for elderly are associated with poorer self-assessment of their QOL (10,11). On the other hand, it has been noticed that elderly people with lower levels of functional independence who lived in their homes rated their QOL better than elderly nursing home residents with higher levels of functional independence (17).

Likewise, research on the QOL of elderly people in nursing homes around the world indicates that women have lower QOL than men (15,18,19). This may be due to sociodemographic factors, lifestyle and level of education, which may explain a significant part of differences in self-assessment of certain QOL domains between women and men (20). However, in most Croatian research conducted in nursing homes, there was no gender related difference in satisfaction with life or in self-assessment of the QOL of the elderly (21,22), as opposed to other countries (15,18-20,23).

According to a study by Havelka *et al.* (24), the need for care services differs with respect to certain examined gerontologic-public health indicators (e.g., age and gender), so that, as expected, people in the older age groups compared to the younger ones have a greater need for all care services. This implies that the elderly with reduced functional independence who are classified as receivers of level 3 social services (with the highest intensity and scope of providing necessary social services) will have their needs better taken care of within 24 hours in institutional care than in their own home, which can have a positive effect on their self-assessment of QOL.

Studies have shown that residents of nursing homes in Croatia assessed their overall QOL as mediocre, and that there was correlation between the aspects of QOL and satisfaction with nursing home services, since residents who were more satisfied with these services assessed their QOL as better (25). To date, no gerontologic research has been carried out linking the self-assessment of the QOL of home residents with the level of social services variable specified in the Ordinance on minimum conditions for the provision of social services by the Ministry of Demographics, Family, Youth and Social Policy (26).

Therefore, the main aim was to investigate whether there is a significant difference in the self-reported domains of the QOL of beneficiaries receiving level 2 *versus* level 3 social services in county-owned nursing homes in the City of Zagreb.

Our research covered self-assessment of the QOL of nursing home residents who are partially dependent on the help of another person to take care of their basic needs (level 2) *versus* those who are functionally dependent on another person to take care of all their needs (level 3). This would improve and balance the quality of care in nursing homes for the elderly with different needs.

PARTICIPANTS AND METHODS

Analytical cross-sectional survey study was carried out successively in 3 county-owned nursing homes in Zagreb (Dubrava, Ksaver and Sv. Josip Nursing Homes) in the period from 2018 to 2019. This survey included 32 respondents receiving level 2 social services and 60 respondents receiving level 3 social services. The residents who wanted and could provide informed consent for the survey were included in the study, covering 27.1% of the residents at level 2 social services and 30.5% at level 3 social services in three nursing homes in Zagreb (Dubrava, Ksaver and Sv. Josip). It should be emphasized that this sample did not overlap with previous research on the QOL of nursing home residents, which predominantly included functionally independent elderly persons (27).

The approval for this study was obtained from the Ethics Committee of the Andrija Štampar Teaching Institute of Public Health.

Participant inclusion/exclusion criteria

Inclusion criteria were as follows: the participants were residents of 3 selected county-owned nursing homes in Zagreb (Dubrava, Ksaver and Sv. Josip Nursing Homes) aged 65 and older who agreed to participate in the study and received level 2 or level 3 social services.

Exclusion criteria were serious health problems that might affect the ability to complete the questionnaire and give informed consent, such as severe psychiatric disorders and severe cognitive impairment (dementia), Alzheimer's disease (moderate/moderately severe phase of the disease), acute illnesses accompanied by high fever, or consciousness disorder.

Instrument

The Quality of Life Scales for Nursing Home Residents 2001 (28) and Barthel Index modified by Shah, Vanclay and Cooper (MBI) (29) structured tests were used to examine residents aged ≥ in 3 county-owned homes in Zagreb. The level of social services was determined by the Ordinance on the minimum conditions for the provision of social services by the Ministry of Demographics, Family, Youth and Social Policy (26). For the Quality of Life Scales for Nursing Home Residents 2001 test, translation from English to Croatian and back translation (for text comparison) from Croatian to English were made. In this study, nursing home residents self-assessed their QOL using a questionnaire which tested the following domains: comfort; functional competence; privacy; dignity; meaningful activity; interpersonal relationships; autonomy; food enjoyment; spiritual well-being; security; and individuality.

The interviews were conducted by persons educated for work with the elderly (physician, social gerontologist, nurse), who are not employees of any of the participating nursing homes. The questionnaire on the sociodemographic status of nursing home residents collected the following general variables on residents from social workers employed at particular nursing home: level of social services they received, age, gender, marital status, educational level, and length of stay in the nursing home.

Statistical analysis

The results were expressed using descriptive statistics methods where the normality of distribution was first tested by the Kolmogorov-Smirnov test. Normally distributed values were expressed by arithmetic mean and standard deviation as an indicator of dispersion, while in the case of deviation from normal distribution, median as the mean and interquartile range were used as dispersion indicator.

To test for group differences, parametric tests were used for normally distributed groups (gaussian curve) of quantitative data (T-test, ANOVA), while non-parametric tests were used to test group differences if the values did not follow normal distribution (Mann-Whitney U, Kruskal-Walis test).

The level of statistical significance was set at α=0.05 and statistical analysis was performed using SPSS 25 software package (IBM, USA).

RESULTS

A total of 92 residents living in three county-owned nursing homes in Zagreb participated in the study. All participants were aged ≥65, divided into three groups (30) by their age: young-old (65-74 years), medium-old (75-84 years) and oldest-old (≥85 years).

Most of the participants (92.3%) were oldest-old and medium-old**,** and the group of the young-old was the smallest, only 7.7%. Of the 92 people included in the study, three-quarters were female (76%) and one quarter were male (24%). As for their marital status, the majority of participants, almost two-thirds, were widows (65.2%) and there were least of those divorced (6.5%). Considering their level of education, the highest number of participants had elementary school education (45.7%) and the least number had undergraduate degree (4.3%). Concerning the level of social services, the highest number of respondents received level 3 (65.2%), followed by level 2 (34.8%) social services. In relation to MBI (29) functional ability, the majority of subjects were totally dependent (36.9%), followed by moderately dependent (32.6%), slightly dependent (18.5%), completely independent (8.7%), and the least number of severely dependent (3.3%) subjects. Considering the length of stay of the participants in nursing homes, the share of those having spent 2-5 years in nursing home was highest (27%), followed by 1-2 years (20%), 5-10 years (16.5%), equal percentage (15.3%) in the categories of 0-6 months and 6 months to 1 year, while 5.9% of the residents had been living in nursing home for 10 or more years.

1. Resident (N=92) self-assessed QOL by tested domains (Table 1) showed the highest level in the domain of individuality (Me=22.80; IQR=12.00-22.80), while the lowest level was determined in the domain of food enjoyment (Me=11.40; IQR=9.02-11.40).

Table 1.
Analysis of self-assessed quality of life of residents (N=92) in 3 county-owned nursing homes (Zagreb, 2018-2019) by tested domains (28)

Quality of life domain	Median	IQR
Comfort (physical)	18.20	15.90-21.00
Functional competence	16.70	7.50-19.00
Privacy	19.00	15.20-19.00
Dignity	19.00	18.20-19.00
Meaningful activity	16.20	11.50-20.15
Interpersonal relationships	13.90	10.10-16.20
Autonomy	15.20	12.82-15.20
Food enjoyment	11.40	9.02-11.40
Spiritual well-being	12.90	10.60-15.20
Security	16.70	14.40-17.00
Individuality	22.80	12.00-22.80

IQR = interquartile range

2. The domains of self-assessed functional competence (Z=5.050), privacy (Z=4.687), meaningful activities (Z=4.632), interpersonal relationships (Z=3.394), autonomy (Z=3.352) and individuality (Z=3.755) (p<0.001 all) were significantly higher among residents receiving level 2 than in those receiving level 3 social services (Table 2).

Table 2.
Comparison of domains of resident (N=92) self-assessed quality of life (28) in 3 county-owned nursing homes (Zagreb, 2018-2019) in relation to the level of social services

	Category 2		Category 3		MW - U*	Z	p
	Me	IQR	Me	IQR			
Comfort (physical)	19.50	(16.78-22.65)	17.50	(15.60-20.90)	727.50	1.141	0.257
Functional competence	19.00	(19.00-19.00)	10.50	(7.50-19.00)	304.50	5.050	<0.001
Privacy	19.00	(19.00-19.00)	16.70	(12.75-19.00)	370.50	4.687	<0.001
Dignity	19.00	(19.00-19.00)	19.00	(18.00-19.00)	751.00	1.848	0.065
Meaningful activity	20.15	(16.75-21.63)	14.45	(9.95-17.59)	314.00	4.632	<0.001
Interpersonal relationships	15.50	(13.30-16.20)	11.60	(10.00-14.00)	540.50	3.394	0.001
Autonomy	15.20	(15.20-15.20)	14.70	(11.45-15.20)	558.00	3.352	0.001
Food enjoyment	11.40	(9.03-11.40)	10.60	(9.03-11.40)	804.00	1.377	0.170
Spiritual well-being	13.10	(12.30-15.20)	12.30	(9.68-15.05)	701.00	1.725	0.085
Security	16.70	(15.83-16.78)	16.70	(14.00-17.45)	780.00	0.810	0.421
Individuality	22.80	(22.80-22.80)	20.50	(12.00-22.80)	519.00	3.755	<0.001

*Mann-Whitney U test
Z = approximate Z value for the corresponding MW U value; IQR = interquartile range

3. Comparison of functional independence (MBI) (29) with the domains of self-assessed QOL revealed a statistically significant difference in the domains of functional competence (H=63.56; p<0.001), privacy (H=17.31; p=0.002) and meaningful activities (H=33.97; p<0.001), where the lowest value was determined in totally dependent residents (Table 3).

Table 3.
*Comparison of domains of resident (N=92) self-assessed quality of life (28) in 3 county-owned nursing homes (Zagreb, 2018-2019) in relation to their functional independence (MBI)**

	Total dependence	Severe dependence	Moderate dependence	Slight dependence	Complete independence	Krus kal-Wallis H**	Df	p
	Me (IQR)	Me (IQR)	Me (IQR)	Me (IQR)	Me (IQR)			
Comfort (physical)	17.40 (15.40-19.70)	21.80 (20.50-23.10)	19.20 (16.40-20.80)	17.70 (15.60-21.65)	22.80 (14.60-22.80)	5.61	4	0.230
Functional competence	7.50 (7.50-7.50)	16.70 (11.00-22.40)	19.00 (14.93-19.00)	19.00 (19.00-19.00)	19.00 (19.00-19.00)	63.56	4	<0.001
Privacy	16.70 (9.75-19.00)	18.20 (15.80-20.60)	19.00 (16.70-19.00)	19.00 (15.85-19.00)	19.00 (19.00-19.00)	17.31	4	0.002
Dignity	19.00 (17.50-19.00)	19.00 (19.00-19.00)	19.00 (17.80-19.00)	19.00 (18.60-19.00)	19.00 (19.00-19.85)	9.16	4	0.057
Meaningful activity	10.00 (9.13-15.15)	22.45 (14.25-30.65)	18.00 (15.00-20.65)	19.40 (15.30-20.90)	20.15 (17.44-22.06)	33.97	4	<0.001
Interpersonal relationships	12.75 (9.00-13.90)	16.00 (14.00-18.00)	13.90 (10.50-16.20)	15.40 (11.80-16.20)	13.90 (9.65-16.20)	6.52	4	0.164
Autonomy	13.40 (11.10-15.20)	15.00 (13.40-16.60)	15.20 (12.90-15.20)	15.20 (15.20-15.20)	15.20 (14.30-15.35)	8.72	4	0.068
Food enjoyment	10.80 (9.00-11.40)	11.40 (10.00-12.80)	11.20 (9.00-11.40)	11.40 (9.00-11.40)	11.40 (9.68-11.40)	3.19	4	0.526
Spiritual well-being	11.35 (8.33-15.00)	12.00 (7.00-17.00)	12.90 (10.60-15.10)	13.40 (11.10-15.20)	13.75 (12.23-15.20)	5.14	4	0.273
Security	16.70 (14.40-18.20)	16.70 (14.00-19.40)	16.50 (14.40-17.05)	16.70 (14.95-16.70)	16.70 (14.00-19.00)	0.69	4	0.952
Individuality	20.50 (12.00-22.80)	17.00 (9.50-24.50)	22.80 (12.00-22.80)	22.00 (13.20-22.80)	22.80 (14.70-22.80)	4.49	4	0.343

*MBI categories: 0-20=total dependence; 21-60=severe dependence; 61-90=moderate dependence; 91-99=slight dependence; 100=complete independence **Kruskal-Wallis test df = degree of freedom; number of categories of independent variable -1 IQR = interquartile range

4. We did not find any significant gender differences in QOL domains (Table 4).

Table 4.
Comparison of domains of resident (N=92) self-assessed quality of life (28) in 3 county-owned nursing homes (Zagreb, 2018-2019) according to gender

	Male		Female		MW - U*	Z	p
	Me	IQR	Me	IQR			
Comfort (physical)	20.00	(17.60-21.90)	17.40	(15.40-20.63)	545.50	1.47	0.144
Functional competence	19.00	(9.50-19.00)	15.00	(7.50-19.00)	568.00	1.40	0.165
Privacy	19.00	(17.45-19.00)	18.20	(15.00-19.00)	584.50	1.24	0.217
Dignity	19.00	(17.08-19.00)	19.00	(18.60-19.00)	709.50	0.52	0.604
Meaningful activity	19.95	(13.38-22.08)	15.90	(11.05-19.40)	489.00	1.78	0.075
Interpersonal relationships	13.90	(9.75-16.20)	13.90	(10.30-16.20)	745.00	0.13	0.898
Autonomy	15.20	(12.00-15.20)	15.20	(12.90-15.20)	705.50	0.43	0.672
Food enjoyment	11.40	(8.83-11.40)	11.40	(9.00-11.40)	712.00	0.57	0.572
Spiritual well-being	12.65	(10.40-13.55)	12.90	(10.60-15.20)	648.50	0.85	0.398
Security	16.70	(12.58-16.70)	16.70	(14.40-17.95)	555.50	1.27	0.207
Individuality	20.50	(12.00-22.80)	22.80	(12.05-22.80)	739.00	0.20	0.847

*Mann-Whitney U test
Z = approximate Z value for the corresponding MW U value; IQR = interquartile range

5. Comparison of self-assessed QOL domains according to age groups revealed a statistically significant difference in the domain of dignity (H=9.696; p=0.008), where lower levels were found in residents of the 85+ age group followed by 75-84 and 65-74 age groups (Table 5).

Table 5.
Comparison of domains of resident (N=92) self-assessed quality of life (28) in 3 county-owned nursing homes (Zagreb, 2018-2019) according to age groups

	65-74		75-84		85+		Kruskal-Wallis H*	Df	p
	Me	IQR	Me	IQR	Me	IQR			
Comfort (physical)	20.00	(14.60-22.80)	18.20	(15.40-20.65)	17.95	(16.35-21.85)	1.134	2	0.567
Functional competence	14.95	(7.50-17.28)	19.00	(7.50-19.00)	16.70	(7.50-19.00)	0.685	2	0.710
Privacy	19.00	(17.83-19.00)	18.20	(14.40-19.00)	19.00	(15.90-19.00)	1.483	2	0.476
Dignity	19.00	(19.00-20.00)	19.00	(19.00-19.00)	19.00	(17.20-19.00)	9.696	2	0.008
Meaningful activity	21.05	(16.68-22.83)	17.30	(11.55-20.23)	15.30	(10.53-20.15)	5.696	2	0.058
Interpersonal relationships	15.60	(13.90-16.20)	13.90	(10.73-16.20)	13.90	(10.00-16.20)	2.566	2	0.277
Autonomy	15.00	(12.90-15.20)	15.20	(13.15-15.20)	15.20	(11.80-15.20)	0.501	2	0.778
Food enjoyment	11.40	(9.00-11.40)	11.40	(9.10-11.40)	11.40	(9.00-11.40)	0.922	2	0.631
Spiritual well-being	12.90	(8.40-13.40)	14.00	(10.60-15.20)	12.90	(9.80-14.70)	2.127	2	0.345
Security	16.70	(16.13-17.00)	16.70	(15.00-18.80)	16.70	(14.20-16.70)	2.899	2	0.235
Individuality	22.80	(12.00-22.80)	22.80	(14.35-22.80)	21.00	(12.00-22.80)	1.303	2	0.521

*Kruskal-Wallis test; IQR = interquartile range

DISCUSSION

The results obtained by analysis of the self-assessed QOL of residents receiving levels 2 and 3 social services in 3 county-owned nursing homes in relation to the variables examined, i.e. age structure, gender, levels of social services, and functional independence categories, showed that statistically significant differences in individual domains were regularly present except for gender (Tables 1-5).

The analysis of resident self-assessed QOL (Table 5) showed that significant age related differences were present in the smallest number of domains (1/11; dignity).

Many domains (6/11; functional competence, autonomy, privacy, individuality, meaningful activities and interpersonal relationships) in resident self-assessment of the QOL were related to the level of social services provided (Table 2). This indicates the crucial role of distributing and delivering the scope and intensity of social services in nursing homes with the aim of focusing gerontologic interventions in order to preserve and improve the quality of resident lives. Distribution by levels of social services in nursing homes was mainly based on the functional independence of the elderly. Consequently, analysis of resident self-assessed QOL in relation to the distribution by categories of functional independence MBI (29) also yielded a statistically significant difference in the number of domains examined (3/11), namely privacy, functional competence, and meaningful activities (Table 3).

The primary objective of determining functional competence (independence) of an elderly person is to determine the degree of ability (independence) in completing certain tasks as part of performing daily activities (such as dressing, walking, eating, etc.) and the need for someone else's help or aids. Standardized measurements, appropriate validity and reliability (31) are applied to determine functional status, depending on the purpose of the assessment and the group we are testing. Consequently, functional competence of the elderly involves assessing the ability to perform all daily activities that ensure appropriate QOL, including biological, psychological and social functioning (30). This is a crucial gerontologic-public health indicator that guides professionals in the health care of the elderly in the application of health and social interventions such as the organizational, institutional or non-institutional care for an individual user (32). Thus, the level of functional independence (objectively determined by medical staff using standardized questionnaires) is particularly relevant for assessing the QOL of elderly persons and for developing integrated gerontologic projects that comprehensively embrace an intersectoral approach to the provision of health and social care services for the elderly (29,32). For example, MBI (29) is frequently used and easy to administer for functional independence assessment for the elderly.

Quality of life assessment requires a multidimensional approach (8,9,12,33,34), which refers to objective descriptors and subjective, comprehensive assessment of well-being over a wide area of functioning of an elderly person (12,32,34). Research points to particularities in assessing the QOL of the elderly, such as the limited utility of using the SF36 questionnaire in nursing homes (28,35). Consequently, for example, the Quality of Life Scales for Nursing Home Residents (University of Minnesota School of Public Health) (28) is used, with domains that primarily cover psychological and social aspects of the QOL, such as physical comfort, privacy, autonomy, dignity, spiritual well-being, and others (28,36).

The QOL of the elderly is connected to the availability and sufficiency of institutional and non-institutional professional assistance needed in the local community (37). In old age, QOL is also affected by the sense of usefulness, degree of activity, a preserved social network and family relationships (14,38). It has been found that the needs for health care services, home care services, and services related to leisure time and activities of the elderly (24) differ with respect to the individual determinants of gerontologic-public health indicators (such as age and gender), and it is expected that people in elderly groups compared to younger groups will have a greater need for all care services.

Studies suggest that the most important aspects of the QOL of nursing home residents are their dignity, spiritual well-being, food enjoyment (39), leisure activities, and independence, but also the impact of family relationships, social life, independence, tranquility and satisfaction (39,40).

The predictors that indicate lower QOL for the elderly in nursing homes are the diagnosis of depression, decreased functionality in daily activities (10,41), neuropsychiatric symptoms of dementia (42), lower socioeconomic status and social support (4,43), cognitive impairment (10), female gender (20,23), multiple comorbidities (43) and an extended stay in the nursing home (4). In particular, it should be noted (44) that depression and difficulty in communicating with staff are two main variable risk factors for poorer QOL of elderly home residents. Consequently, it can be concluded that many studies in nursing homes indicate that resident self-assessment of the QOL across the examined domains differ with respect to gender, functional independence, mental health, represented health problems, and other factors (10,11,16,23,45).

In this study, self-assessment of the QOL in residents receiving level 2 and level 3 social services showed that the lowest level was in the domain of food enjoyment (Table 1), which indicating the need for necessary interventions in the implementation of gerontologic nutritional standards and menus in nursing homes.

The results of this study looking into differences in the examined domains of self-assessed QOL of the elderly, e.g., meaningful activities (Table 2), indicate the need for the application of targeted gerontologic interventions such as appropriate occupational therapy in accordance with personal preferences, health status, and level of functional independence for residents receiving level 3 social services. Such gerontologic interventions refer to the improvement of health and social services for residents, which would result in improving the aspect of satisfaction with nursing home services directly related to their QOL (25). Consequently, the established connection between the level of social services of nursing home residents and their self-assessed QOL suggests the need for further research paying special attention to mental health and verified diagnoses of the residents.

The limitations of this study were that the study did not include groups of residents receiving level 4 social services in nursing homes, which includes residents with dementia, Alzheimer's disease (moderate/moderately severe phase of the disease) because of a significant problem in communication and their testing. Thus, subjects with severe cognitive impairments and other severe psychiatric disorders were not included, which could have an impact on the results across the QOL domains. Also, the impact of chronic illnesses of residents that could affect their self-assessment of QOL was not examined (45,46). Undoubtedly, many variables such as family relationships, length of stay in nursing home, or depression are relevant and can greatly affect the life satisfaction of the elderly, but go beyond the scope of this research and represent a limitation of this study.

The number of participants in this study was not representative of private nursing homes, which show great diversification in the possibilities of providing social services.

Also, residents who are accommodated in the so-called residential part of nursing homes and classified as level 1 social service users, meaning that they were fully functionally independent, were not included in the survey. Results of a previous study on self-assessment of QOL conducted on 150 residents, of which more than 50% were fully functionally independent according to the MBI, show the lowest estimated domain of physical comfort and sense of security (Maksimir, Pešćenica and Sv. Josip Nursing Homes, Zagreb, HR) (2017-2018) (27).

CONCLUSION

Research on the association between selected gerontologic-public health indicators such as levels 2 and 3 social services provided, category of functional independence (MBI), age, gender and QOL of the elderly is important because of the opportunities for improving the individual gerontologic approach with a recommendation for greater adaptability towards residents who are completely dependent on another person's help.

The results of this study demonstrate a significant difference in the examined domains of self-assessed QOL between residents of nursing homes who are partially *versus* totally dependent on the assistance of others (levels 2 and 3 social services), and at the same time guide the gerontologic multidisciplinary team in selecting focused interventions that can contribute to improving the QOL of the elderly.

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SAŽETAK

SAMOPROCIJENJENA KVALITETA ŽIVOTA KORISNIKA KOJI PRIMAJU 2. i 3. STUPANJ SOCIJALNIH USLUGA U DECENTRALIZIRANIM DOMOVIMA ZA STARIJE U GRADU ZAGREBU

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Cilj je bio analizirati postoji li značajna razlika u samoprocjeni ispitivanih domena kvalitete života korisnika koji primaju drugi stupanj socijalnih usluga naspram korisnika koji primaju treći stupanj socijalnih usluga u decentraliziranim domovima u Gradu Zagrebu. Analitičko presječno istraživanje sukcesivno je provedeno 2018.-2019. godine u tri decentralizirana doma za starije u Gradu Zagrebu uključujući korisnike domova za starije koji primaju 2. i 3. stupanj socijalnih usluga. Pomoću testa *Quality of Life Scales for Nursing Home Residents* 2001. ispitana je samoprocjena kvalitete života kod 92 korisnika u dobi od ≥65 godina, dok je za procjenu njihove funkcionalne samostalnosti korišten Barthel indeks modificiran prema Shah, Vanclay i Cooper (MBI). Korištene su opće sociodemografske varijable uključujući i stupanj socijalnih usluga. Samoprocjena domena funkcionalne sposobnosti (Z=5,050), privatnosti (Z=4,687), smislene aktivnosti (Z=4,632), međuljudskih odnosa (Z=3,394), autonomije (Z=3,352) i individualnosti (Z=3,755) (p<0,001 sve) bila je značajno veća kod korisnika koji primaju 2. stupanj socijalnih usluga u odnosu na korisnike koji primaju 3. stupanj socijalnih usluga. Samoprocijenjena kvalitete života korisnika (N=92) pokazala je najnižu razinu u domeni uživanja u hrani (Me=11,40; IQR=9,02-11,40). Razlika u ispitivanim domenama samoprocijenjene kvalitete života između korisnika 2. i 3. stupnja socijalnih usluga u domovima za starije usmjerava intervencije gerontološkog multidisciplinskog tima koje mogu doprinijeti poboljšanju kvalitete života starijih osoba, i to poglavito za funkcionalno ovisne kojima je potrebna pomoć druge osobe u punom opsegu (3. stupanj socijalnih usluga). Samoprocijenjena kvaliteta života korisnika koji primaju 2. i 3. stupanj socijalnih usluga pokazala je najnižu razinu u domeni uživanja u hrani, što upućuje na potrebu nužnih intervencija u primjeni gerontološko prehrambenih normi i jelovnika domova za starije osobe.

Ključne riječi: **funkcionalna samostalnost, domovi za starije, samoprocjena kvalitete života, starije osobe**

VAŽNOST OPTIČKE KOHERENTNE TOMOGRAFIJE MAKULE U NEUROOFTALMOLOGIJI

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Cilj: Sloj vlakana vidnog živca (RNFL, engl. *retinal nerve fiberlayer*) čine aksoni retinskih ganglijskih stanica. Optička koherentna tomografija (OCT, engl. *optical coherence tomography*) važan je alat u dijagnostici optičkih neuropatija. Za procjenu osjetljivosti pretrage izolirano se snimao samo RNFL i posebno se uključila analiza sloja ganglijskih stanica (GCL, engl. *ganglion cell layer*) u makuli. ***Metode:*** Ovo je retrospektivna analiza snimki OCT-a u 348 pacijenata koji su pod sumnjom na optičku neuropatiju upućeni u neurooftalmološki kabinet, u razdoblju od godine dana. OCT snimke dobivene su uređajem SOCT Copernicus REVO *(Optopol TechnologySp. z.o.o.; softver* verzija 7.0.0). ***Rezultati:*** Osjetljivost mjerenja RNFL-a je 37,6 % (62/165) (uz 95 %-tni interval pouzdanosti (CI) 30,2 % - 45,4 %), a dijagnostička točnost testa je 58,6 % (165/292) (CI 95 %: 52,7 % - 64,3 %). Ako se uzme u analizu i GCL čak su 103 pacijenta (35.2 % - 103/292) analizirajući samo RNFL bila lažno negativna, odnosno bez GCL ne bi se otkrila optička neuropatija. ***Zaključak:*** OCT je postalo važno pomagalo u neurooftalmološkoj praksi. Omogućava vizualizirati aksonalni/ neuronalni integritet vidnog puta. Upotreba OCT-a makule uz analizu GCL dovela je do dodatnog proširenja primjenljivost OCT-a u neurooftalmologiji.

Ključne riječi: optička koherentna tomografija, optička neuropatija, retinske ganglijske stanice

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UVOD

Optička koherentna tomografija (OCT, engl. *optical coherence tomography*) je kao neinvazivna dijagnostička metoda postala neophodno pomagalo u otkrivanju i praćenju optičkih neuropatija. OCT-om optičkog diska može se kvantificirati debljina sloja vlakana vidnog živca (RNFL, engl. *retinal nerve fiberlayer*). Upotreba OCT-a makule dovela je do toga da se upotrebljivost OCT-a u neurooftalmologiji dodatno proširi, a naročito od kada se *spectral-domain* OCT-om (SD-OCT, engl. *spectral-domain optical coherence tomography*) povećala rezolucija uz mogućnost segmentacije retinskih slojeva u makuli (1).

RNFL čine aksoni retinskih ganglijskih stanica koji se ujedinjuju na optičkom disku čineći vidni živac. Samo su u području makule ganglijske stanice vidnog živca smještene u više slojeva, za razliku od ostalog dijela retine gdje su samo u jednom sloju. Uz to u području makule nema velikih krvnih žila i glijalnih elemenata koji utječu na peripapilarnu debljinu RNLF-a (2,3). Upravo zbog takve anatomske građe makule može se makularnim OCT-om otkriti rani gubitak ganglijskih stanica, koji se još ne manifestira stanjenjem RNFL-a na optičkom disku.

CILJ RADA

Cilj rada je procijeniti osjetljivost mjerenja samo RNFL-a izolirano, te uz RNFL analizirati i sloj ganglijskih stanica (GCL, engl. *ganglion cell layer*) u makuli upotrebom OCT-a u otkrivanju optičkih neuropatija različite etiologije.

METODE

Ovo je retrospektivna analiza snimki OCT-a 348 pacijenta (198 žena i 159 muškaraca; prosječna dob 57 godina – raspon od 13 do 87 godina) koji su bili upućeni u neurooftalmološki kabinet na Klinici za oftalmologiju Kliničkog bolničkog centra Rijeka pod sumnjom na optičku neuropatiju u trajanju od jedne godine. OCT snimke dobivene su uređajem SOCT Copernicus REVO (*Optopol Technology Sp. z.o.o.*, Poljska; softver verzija 7.0.0). Jedan ispitivač snimio je sve OCT snimke analizirajući RNFL i GCL. Od 348 pacijenata koji su bili pregledani u neurooftalmološkom kabinetu kod 109 nije utvrđena optička neuropatija i imali su urednu debljinu RNFL i GCL.

Kriterij uključenja: dobivene smo rezultate razvrstali u dvije skupine:

1) Skupina u koju su uvrštene optičke neuropatije bez obzira na etiologiju, uz tri podskupine: a) stanjenje RNFL-a uz normalnu debljinu ganglijskih stanica, b) stanjenje RNFL-a uz stanjenu debljinu ganglijskih stanica, te c) pacijenti kojima je RNFL uredne debljine, ali im je stanjen GCL.
2) Zadebljanje RNFL-a zbog edema optičkog diska, različite etiologije, sa zadebljanim, normalnim i stanjenim GCL.

Kriteriji isključenja: visoki miopi (više od -6.00 dioptrija sfere), makulopatije, dijabetička retinopatija, glaukom.

Statistička obrada podataka

Valjanost dijagnostičkih metoda odnosno valjanost dijagnostičkih parametara analizirana je pomoću osjetljivosti i specifičnosti. Osjetljivost je vjerojatnost pozitivnog nalaza uz uvjet prisutnosti bolesti, a specifičnost je vjerojatnost negativnog nalaza uz uvjet odsutnosti bolesti. Analizom dobivenih podataka procijenili smo osjetljivost i specifičnost mjerenja izolirano RNFL-a uz 95 %-tni interval pouzdanosti (CI, engl. *confidence interval*). Dodatno smo odredili osjetljivost i specifičnost GCL. Statistička analiza napravljena je pomoći *Med-Calc* (verzija 18.5; https://www.medcalc.org).

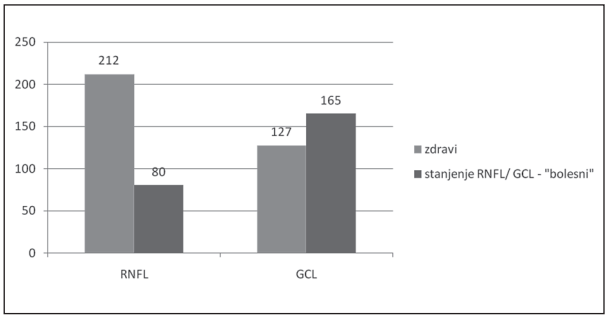
REZULTATI

U prvu su skupinu uključena 183 pacijenta sa stanjenjenjem samo RNFL-a, sa stanjenjem RNFL-a i GCL ili samo sa stanjenjem GCL. U 62 pacijenta izmjereno je stanjenje RNFL-a i GCL, u18 pacijenata samo stanjenje RNFL-a, a kod 103 pacijenta nađeno je stanjenje samo GCL.

Osjetljivost mjerenja RNFL-a je svega 37,6 % (62/165) (uz 95 %-tni CI 30,2 % - 45,4 %), a specifičnost 85,83 % (109/127) (uz 95%-tni CI 78,53 % - 91,38 %).

Za razliku od mjerenja RNFL-a, osjetljivost mjerenja GCL je 100 % (165/165) (uz 95 %-tni CI 97,79 % - 100,00 %), a specifičnost također 100 % (109/109) (uz 95 %-tni CI 96,67 % - 100,00 %).

Kod čak 103 pacijenta (35,2 % - 103/292), analizirajući samo RNFL ne bi se dokazala optička neuropatija, odnosno bili su lažno negativni. Tek analizom GCL u makuli uočeno je stanjenje unutrašnjih retinskih slojeva, uz urednu debljinu RNFL-a na optičkom disku (sl. 1).



Sl. 1. *Optičke neuropatije („bolesni“) dijagnosticirane analizirajući SAMO sloj vlakana vidnog živca (RNFL, engl. retinal nerve fiber layer) i optičke neuropatije („bolesni“) dijagnosticirane analizirajući i sloj ganglijskih stanica (GCL, engl. ganglion cell layer).*

RASPRAVA

Tradicionalno se u neurooftalmologiji OCT-om mjerila debljina RNFL-a pokušavajući povezati stanjenje RNFL-a s depresijom retinske osjetljivosti u određenom dijelu vidnog polja (4). Teorijski, pretpostavljalo se da će stupanj stanjenja RNFL-a imati značajnu povezanost s funkcijom vidnog živca u pacijenata s gubitkom aksona, a manju korelaciju strukture s funkcijom gdje su aksoni još uvijek vitalni, ali trenutno nisu u funkciji, kao npr. kod kompresivne optičke neuropatije ili akutnog optičkog neuritisa (5-12).

Razvojem OCT tehnologije danas se pomoću SD-OCT-a može mjeriti sloj ganglijskih stanica u makuli. Kako se većina retinskih ganglijskih stanica nalazi u makuli, njihov gubitak pomaže u detekciji oštećenja vidnog živca (1). Time je analiza GCL postala važno pomagalo u neurooftalmologiji. Oštećenje GCL-a puno bolje korelira s ispadom u vidnom polju, može predvidjeti progresiju oštećenja vidnog živca, a smatra se i značajnim biomarkerom neurodegeneracije kod multiple skleroze, Alzheimerove bolesti i Parkinsonove bolesti (13).

Ranije se smatralo da kod postgenikulatnih oštećenja vidnog puta odraslih ne dolazi do transgenikulatne retrogradne degeneracije s posljedičnom atrofijom vidnog živca. Analiza ganglijskih stanica omogućila je novi pogled na transsinaptičku degeneraciju vidnog sustava. Sve je više dokaza da kod postgenikulatne hemianopsije dolazi do retrogradne transsinaptičke degeneracije sloja retinskih ganglijskih stanica koja topografski korelira s hemianoptičkim ispadom na vidnom polju, odnosno dolazi do stanjenja GCL u nazalnom dijelu hemiretine na jednom, a u temporalnom na drugom oku (14-19). Takva topografska korelacija ne može se utvrditi analizirajući samo RNFL na optičkom disku.

Klinička interpretacija mogućeg oštećenja aksona postaje još teža kod stanja koja uzrokuju edem optičkog diska. U stanjima koja uzrokuju edem optičkog diska u sklopu npr. idiopatske intrakranijske hipertenzije (IIH), kompresivne optičke neuropatije ili prednje ishemičke optičke neuropatije dolazi do edema unutar aksona što može maskirati razvoj atrofije. Upravo se to može uočiti u drugoj skupini, u koju je bilo uključeno 56 pacijenata s edemom optičkog diska, odnosno zadebljanjem RNFL-a. Zbog edema unutar aksona vidnog živca isključuje se mogućnost detekcije stanjenja RNFL-a i jedina raspoloživa metoda detekcije razvoja atrofije preostaje snimanje sloja ganglijskih stanica u makuli s obzirom da sloj vlakana vidnog živca doprinosi vrlo malo u ukupnoj debljini makule. U 28 od ukupno 56 pacijenata uočeno je stanjenje GCL još za vrijeme postojanja zadebljanja RNFL-a. Već se u akutnoj fazi, za vrijeme edema optičkog diska moglo dokazati razvoj oštećenja vidnog živca koji se izoliranim mjerenjem RNFL-a ne bi mogao prikazati. Zato je kod IIH preciznije pratiti stanjenje GCL nego pratiti oteklinu RNFL-a koja se može smanjivati zbog terapije, ali i razvoja atrofije (13,20,22).

I kod druza optičkog diska puno točniju informaciju daje nam analiza GCL kao rani strukturni pokazatelj nepovratnog neuralnog gubitka (13).

Analiza ganglijskih stanica mnogo bolje korelira s poremećajem vidne funkcije, kao što je to npr. vidna oštrina, kontrastna osjetljivost, te ispadi u vidnom polju. Bolje korelira i s nastankom tjelesnog invaliditeta u bolesnika s multiplom sklerozom i s nalazom na magnetskoj rezonanciji nego samo mjerenje debljine sloja vlakana vidnog živca (23,24).

Slična usporedba analiziranih parametara, prema nama dostupnoj literaturi, nije učinjena.

Ograničenja ovog rada uključuju: kvalitativne kriterije i činjenicu da optičke neuropatije nisu klasificirane prema etiologiji.

ZAKLJUČAK

Stanjenje GCL nađeno na SD-OCT bolji je pokazatelj ranih strukturnih oštećenja nego stanjenje RNFL-a te se može koristiti kao rani biomarker za strukturna oštećenja. Stoga se u kliničkom radu ne bi trebalo ograničiti samo na analizu optičkog diska i RNFL-a, nego kod sumnje na optičku neuropatiju redovito tražiti i analizu GCL-a.

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SUMMARY

IMPORTANCE OF MACULAR OPTICAL COHERENCE TOMOGRAPHY IN NEURO-OPHTHALMOLOGY

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Aim: **The retinal nerve fiber layer (RNFL) is made up of retinal ganglion cell axons. We evaluated sensitivity of optical coherence tomography (OCT) when measuring only RNFL or when a ganglion cell layer (GCL) analysis is added to the evaluation of optic neuropathy.** ***Methods:*** **This was a retrospective analysis of OCT in 348 patients examined at the neuro-ophthalmology department for suspicion of optic neuropathy during one year. OCT scans were taken with SOCT Copernicus REVO (Optopol Technology Sp. z.o.o.; software version 7.0.0).** ***Results:*** **Sensitivity of measuring RNFL alone was 37.6% (62/165) (with 95% confidence interval (CI) 30.2%-45.5%) with 58.6% accuracy (165/292) (CI 95%: 52.7%-64.3%). When taking GCL in analysis, 103 patients (35.2%; 103/292) would be classified as normal, false-negative if just RNFL measurements would be the only criterion for diagnosing optic neuropathy.** ***Conclusions:*** **OCT has become one of the most important tools in neuro-ophthalmic practice. It allows us to visualize axonal/neuronal integrity in the afferent visual pathway. Use of macular OCT with GCL analysis has contributed to the extended applicability of OCT in neuro-ophthalmology.**

Key words: **optical coherence tomography; optic nerve disease; retinal ganglion cells**

COVID-19: NAŠA PRVA TERAPIJSKA ISKUSTVA

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Cilj: Iznenadna pojava epidemije koronavirusne bolesti 2019 (COVID-19) uzrokovane koronavirusom 2 teškog akutnog respiratornog sindroma (SARS-CoV-2) zatekla je zdravstvene sustave širom svijeta potpuno nespremne, i svi terapijski pokušaji liječenja bolesti danas su još uvijek na razini kliničkih ispitivanja ili empirijskih terapija, pa su i terapijski ishodi različiti. Među lijekove koji se danas koriste u brojnim randomiziranim kliničkim studijama spadaju i klorokin, jedan stari antimalarik, i tocilizumab, prvi blokator interleukina-6 na tržištu. Cilj ovoga rada bio je prikazati naša prva iskustva u terapiji COVID-19 infekcije s tim lijekovima. ***Metode:*** U razdoblju od 10. 3.- 9. 5. 2020. u zadarskoj županiji registrirano je 85 osoba s pozitivnim nalazom na SARS-Cov-2 koronavirus metodom polimerazne lančane reakcije u realnom vremenu (RT-PCR) od kojih je 31 (36,5 %) hospitalizirano. U 27 (87,1 %) bolesnika kao početna terapija primijenjen je klorokin, a u 3 (9,6 %) kombinacija lopinavir/ritonavir. ***Rezultati:*** 5 bolesnika (16,1 %) iz skupine liječenih klorokinom premješteno je u JIL zbog progresije bolesti i potrebe za mehaničkom ventilacijom, a troje (9,6 %) od njih liječeni su tocilizumabom, s dobrim terapijskim ishodom u svih. ***Zaključak:*** Rezultati liječenja naših bolesnika upućuju na potrebu ranog uključivanja klorokina u terapijski protokol COVID-19 infekcije, ali i ranijeg uključivanja tocilizumaba u terapiju teških bolesnika, kako bi se spriječila progresija bolesti.

Ključne riječi: SARS-CoV-2, COVID-19, klorokin, tocilizumab, antibiotici

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UVOD

COVID-19 pandemiju, uzrokovanu SARS-Cov-2 virusom iz porodice beta-koronavirusa, koja je započela krajem 2019. godine u Wuhanu (glavni grad pokrajine Hubei u Kini), odlikuje visoka stopa morbiditeta i mortaliteta te nepostojanje specifičnog lijeka i cjepiva za tu bolest (1). Time su svi terapijski protokoli svedeni na pokušaje kontrole infekcije raznim antivirusnim lijekovima, kontrole sekundarnih bakterijskih infekcija, kontrole inflamatornog odgovora i mogućih komplikacija, a kontrola epidemije svedena je na dijagnostiku i mjere izolacije bolesnika i zaraženih osoba.

Svjetska zdravstvena organizacija (SZO) je 8. prosinca 2015. godine objavila popis od 8 patogena koji mogu uzrokovati velike epidemije u budućnosti. U tih 8 patogena spadaju i korona virusi SARS-a (*Severe Acute Respiratory Syndrome*), uzročnika epidemije krajem 2002. godine koja se proširila na 37 zemalja, MERS-a (*Middle Eastern Respiratory Syndrome*), uzročnika epidemije 2012. godine koja se proširila na 27 zemalja, te virus Ebole, uzročnika epidemije krajem 2013. godine sa širenjem u 10 zemalja (2). Nažalost, u svim tim slučajevima i nakon brojnih kliničkih ispitivanja nije ni do danas pronađen specifični lijek, a specifično cjepivo odobreno je tek za virusnu infekciju Ebola 2019. godine.

Danas, šest mjeseci od početka pandemije uzrokovane SARS-CoV-2 virusom, još uvijek nema specifičnog lijeka (ni cjepiva) za COVID-19, a diljem svijeta u tijeku su brojna randomizirana klinička ispitivanja različitih lijekova, od antivirusnih do imunomodulacijskih.

COVID-19 je akutna respiratorna bolest i glavni način širenja je kapljičnim putem, respiratornim sekretima i izravnim kontaktom. Neodređeni postotak osoba inficiranih SARS-CoV-2 virusom ostaju asimptomski nosioci virusa. U oboljelih se najčešće nakon inkubacije od nekoliko dana (3-7) javljaju simptomi vrućice, kašlja, malaksalosti, iskašljavanja, kratkoće daha, te grlobolja i glavobolja; u manjeg broja bolesnika razvijaju se i gastrointestinalni simptomi s proljevom, povraćanjem (3). U starijih osoba i onih s kroničnim bolestima pluća, srca, dijabetesom, hipertenzijom, može doći do brzog razvoja akutnog respiratornog distress sindroma (ARDS), poremećaja koagulacije, septičkog šoka, multiorganskog zatajivanja i smrti (4).

Lijekovi koji se koriste u brojnim kliničkim ispitivanjima u COVID-19 infekciji (više od 350 aktivnih studija do početka travnja 2020.) su:

- antivirusni lijekovi kao analog guanina favipiravir, inhibitor RNK polimeraze; kombinacija lopinavira i ritonavira, inhibitor proteaze koji se koristi u HIV-1 infekciji; analog adenina remdesivir, inhibitor virusne RNK polimeraze, koji je pokazao značajni antivirusni učinak u terapiji Ebola infekcije (5), i najbolje rezultate u dosadašnjim kliničkim ispitivanjima SARS-CoV-2 infekcije (6)
- klorokin, također s određenim antivirusnim učinkom (7)
- različiti antibiotici za sekundarne bakterijske infekcije, te
- anticitokinski lijekovi kao tocilizumab, koji blokira receptore interleukina - 6 (IL-6) i time snažnu inflamatornu reakciju koja se pojavljuje u teškim oblicima COVID-19 infekcije (8).

Klorokin je 4-aminokinolin koji je "u uvjetima *in vitro*" pokazao antivirusni učinak na veći broj RNA (15), ali i neke DNA viruse (2); to, međutim, nije definitivno potvrđeno u brojnim kliničkim ispitivanjima, vjerojatno zbog složene farmakodinamike klorokina i pitanja koncentracije lijeka koja bi bila odgovarajuća onoj "u uvjetima *in vitro*" (9). I u slučaju SARS-CoV-2 virusne infekcije neka su "u uvjetima *in vitro*" klinička ispitivanja pokazala dobar klinički odgovor na klorokin (10,11). Danas je širom svijeta registrirano više od 80 kliničkih ispitivanja klorokina (klorokin fosfata i hidroksiklorokina), sa ili bez drugih lijekova, što bi nakon dobro planiranih i kontroliranih randomiziranih studija moglo dovesti do konačnog zaključka o antivirusnoj učinkovitosti klorokina.

Početne studije u COVID-19 bolesnika u kojih je došlo do razvoja akutnog respiratornog distres sindroma (ARDS), kao i patoanatomske studije u umrlih bolesnika pokazale su imunološki poremećaj u smislu hiperaktivacije humoralne imunosti preko proinflamatornog citokina IL-6 i hiperaktivacije citotoksičnog T-staničnog odgovora (12,13). Jedna je sistematska meta-analiza pokazala dobar učinak blokade IL-6 receptora i time hiperaktivne imunološke reakcije, tzv. citokinske oluje, ciljanim monoklonskim antitijelom tocilizumabom (14).

U ovom radu prikazujemo rezultate retrospektivnog, nekontroliranog i nekomparativnog ispitivanja u bolesnika s COVID-19 infekcijom liječenih klorokinom, s antibiotikom ili bez njega.

METODE

Bolesnici i dijagnostika

Od 85 osoba s pozitivnim nalazom na SARS-CoV-2 RNA metodom polimerazne lančane reakcije u realnom vremenu (RT-PCR, *real-time polymerase chain reaction*) u istodobno uzetim brisevima nazofarinksa i ždrijela na osnovi anamneze i kliničkih simptoma i znakova bolesti hospitaliziran je 31 bolesnik; jedan asimptomatski bolesnik primljen je zbog potrebe neurokirurškog zahvata. Među SARS-CoV-2 pozitivnima bilo je 5 djece od 4 do 11 godina (nijedno dijete nije hospitalizirano).

Klinička klasifikacija i praćenje

Od bolesnika su uzeti anamnestički podatci o pojavi simptoma bolesti, rizičnim čimbenicima infekcije, kao i podatci o kroničnim bolestima. Prema težini infekcije bolesnici su pripadali svim 5 skupinama: asimptomatski, lakši, umjereni, teški i kritični (15).

Uz rutinske laboratorijske nalaze (kompletna krvna slika, diferencijalna krvna slika, C-reaktivni protein, prokalcitonin, GUK, D-dimer, aminotransferaze i druge), u slučaju progresije bolesti korištena je i koncentracija interleukina-6 (IL-6).

U svih je bolesnika učinjen rendgenski (RTG) pregled pluća, a u manjeg broja (uglavnom teških bolesnika) i CT (kompjutorizirana tomografija) pluća.

Liječenje

Bolesnici su u početku liječeni većinom (27) klorokinom ili kombinacijom klorokina i doksiciklina (u bolesnika s pneumonijom), a u manjeg je broja (3) početna terapija bila kombinacija lopinavir/ritonavir (3, tj. 10 %); jedan bolesnik s asimptomskom infekcijom nije liječen.

Liječenje klorokin fosfatom (peroralno): bolesnici su dobivali 2×500 mg do 10 dana (22 bolesnika) ili 1500 mg prvi dan i dalje 1000 mg/dan još 4 dana (5 bolesni-

ka), s doksiciklinom ili bez njega, ovisno o radiološkom dokazu pneumonije. Ni u jednog bolesnika nisu zabilježene kontraindikacije za terapiju (npr. srčana, dekompenzacija, terminalna renalna insuficijencija, anemija, hipoglikemija…).

U troje bolesnika korištena je kombinacija lopinavir/ritonavir, u dvoje s blažom infekcijom, i u trećeg s teškom infekcijom i kontraindikacijom za terapiju s klorokinom (teža kardiomiopatija).

U pet bolesnika s brzom progresijom pneumonije i razvojem respiratorne insuficijencije korištena je uz klorokin i kombinacija teikoplanina i beta-laktama (penema), a u troje od njih (prije nastanka akutnog respiratornog distres sindroma, ARDS-a) korištena je i terapija anti-IL-6 monoklonskim antitijelom (tocilizumab).

Kriteriji kod otpusta

Kriteriji za otpust iz bolnice bili su uz kliničko poboljšanje i nalaz 2 RT-PCR negativna brisa nazofarinksa na SARS-CoV-2 RNK u razmaku od 48 sati.

REZULTATI

U razdoblju od 10. 3. do 9. 5. 2020. u zadarskoj županiji učinjena su 1983 testiranja na SARS-Cov-2 koronavirus, 85 osoba bilo je pozitivno, od kojih je 31 osoba hospitalizirana. Prosječna dob hospitaliziranih bolesnika bila je 62,7 godina (od 20 do 87 godina), podjednako muškog i ženskog spola (51,6 %/48,4 %), starijih od 65 godina 41,9 %, a od komorbiditeta rizičnih za teže oblike infekcije najčešće se radilo o hipertenziji (48,4 %) (tablica 1).

Tablica 1
Demografska obilježja i komorbiditeti hospitaliziranih COVID-19 bolesnika (N=31)

Obilježje	Broj (%)
Dob	
Prosječna 62,7 godina Raspon (min-maks) 20-87 godina >65 godina	 13 (41,9)
Spol	
Muški Ženski	16 (51,6) 15 (48,4)
Komorbiditeti	
Arterijska hipertenzija Dijabetes Kardiomiopatija Astma Ostalo*	15 (48,4) 3 (9,6) 3 (9,6) 2 (6,6) 9 (29,0)

*Hipotireoza, demencija, gastritis, reumatoidni artritis, aortna stenoza

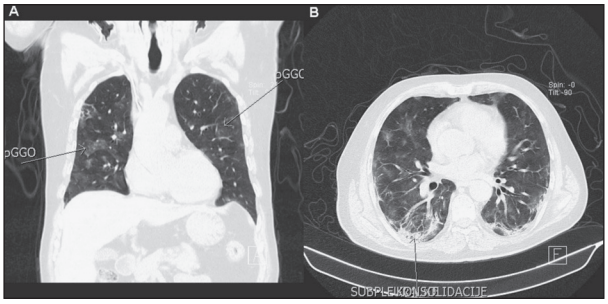
U odnosu na težinu bolesti, najčešće se radilo o umjereno teškim kliničkim oblicima (51,6 %) s radiološki dokazanim pneumonijama, a jedna osoba je primljena bez simptoma infekcije (zbog potrebe neurokirurškog zahvata). Najčešći simptomi bili su vrućica (73,3 %) i kašalj (80,0 %), a anosmija je zabilježena u 3 bolesnika (10 %). Većina bolesnika zaprimljena je u prvom tjednu bolesti (24, tj. 80 %). Hipoksemija s potrebom terapije kisikom zabilježena je u 19 (61,3 %) bolesnika (tablica 2).

Tablica 2.
Klinička obilježja hospitaliziranih COVID-19 bolesnika (N=31)

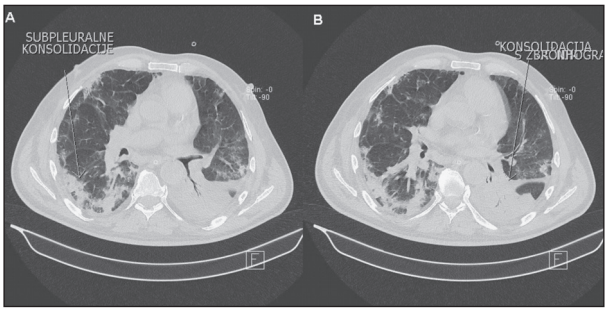
Obilježje	N (%)
Klinički oblici bolesti	
Asimptomski Blagi Umjereni Teški Kritični	1 (3,2) 8 (25,8) 16 (51,6) 1 (3,2) 5 (16,1)
Simptomi	
Vrućica Kašalj Umor Mialgija Kratki dah Anosmija	22 (78,3) 24 (80,0) 15 (30,0) 8 (26,6) 8 (26,6) 3 (10,0)
RDG pluća	
Pneumonija prisutna Pneumonija odsutna	19 (61,3) 12 (38,7)
Terapija kisikom	19 (61,3)
Premješteni u JIL	5 (16,1)

Od laboratorijskih nalaza kod prijma leukopenija je zabilježena u 4 (12,9 %) bolesnika, limfopenija u 7 (22,6 %), povišene vrijednosti CRP u 25 (80,6 %) bolesnika i povišene vrijednosti D-dimera u 8 (25,8 %) bolesnika; u jednog kritično teškog bolesnika zabilježene su izrazito povišene vrijednosti IL-6.

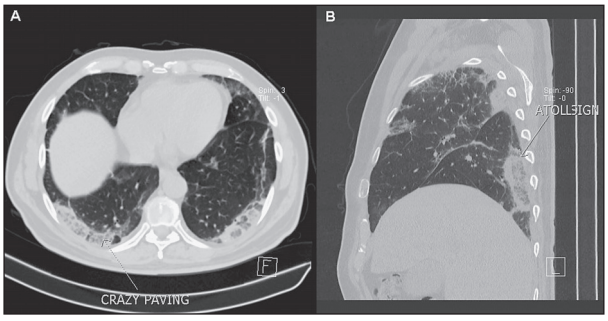
Prosječno trajanje hospitalizacije bilo je 12,4 dana, a samo u jednog bolesnika (3,2 %) dogodio se smrtni ishod (bolesnik u dobi od 88 godina s teškom kardiomiopatijom i početnom terapijom lopinavir/ritonavir). Potreba za drugom antibiotskim terapiju zbog progresije pneumonije zabilježena je u 5 bolesnika (16,1 %) i kod njih je korištena kombinacija teikoplanina i beta-laktama. U troje kritičnih bolesnika s brzom progresijom pneumonije (sl. 1-3) i razvojem respiratorne insuficijencije, koji su premješteni u Jedinicu intenzivnog liječenje (JIL) na mehaničku ventilaciju, korišten je tocilizumab s vrlo dobrim ishodom u sve trojice (tablica 3). Nisu zabilježene značajnije nuzpojave ni kod primjene klorokina, ni tocilizumaba.



Sl. 1. *A-MSCT toraksa: posterobazalnim područjima donjih plućnih režnjeva prisutni su subpleuralni konsolidati (označeno). B-Zone čistog "zrnatog stakla" (označeno) duž ostatnih dijelova donjih i gornjih plućnih režnjeva obostrano.*



Sl. 2. *A- MSCT toraksa: subpleuralni, multilobularni, konsolidati desno (označeno). B-Konsolidacija ss zračnim bronhogramom u donjem plućnom režnju lijevo(označeno).*



Sl. 3. *MSCT toraksa: organizirajuća pneumonija*

Tablica 3.
Terapija i ishod u hospitaliziranih COVID-19 bolesnika (N=31)

Obilježje	N (%)
Početak terapije u odnosu na prve simptome bolesti	
Dan 1-3	11 (36,6)
Dan 4-7	13 (43,3)
Dan >7	6 (20,0)
Duljina hospitalizacije	
Median	12,4
Raspon (min-maks)	2-42
Otpušteni	30 (96,7)
Umrli	1 (3,2)
Početna terapija	
Klorokin	8 (25,8)
Klorokin/doksiciklin	19 (61,3)
Lopinavir/ritonavir	3 (9,6)
Drugi antibiotici	
Teikoplanin/Imipenem	5 (16,1)
Ceftriakson	2 (6,4)
Koamoksiklav	1 (3,2)
Diflukan	4 (12,9)
Ciprofloksacin	1 (3,2)
Druga terapija	
Tocilizumab	3 (9,6)

RASPRAVA I ZAKLJUČCI

Slično nekim drugim studijama (16,17), i u našoj seriji bolesnika se većinom radilo o blažim i umjerenim oblicima bolesti (tablica 2). Prosječno vrijeme od početka simptoma do prijma i početka terapije bilo je u većine bolesnika unutar prvog tjedna bolesti, a s obzirom da se radilo uglavnom o blažim i umjereno teškim oblicima bolesti glavni je cilj terapije bio izbjeći progresiju u teže oblike.

Rendgenski se u naših bolesnika s pneumonijom većinom radilo o obostranoj pneumoniji, što je češće u težim slučajevima (4,18). Pneumonija u naših bolesnika nije dokazana u više od trećine bolesnika (38,7 %) bez obzira na respiratorne simptome u većine, na što je također upozoreno u većim serijama bolesnika (19). Pokazalo se da je CT znatno senzitivnija pretraga i zabilježene su promjene čak i u asimptomskih COVID-19 bolesnika (20), mada i odsutnost CT promjena i u blažih i težih bolesnika (14). Najčešće promjene su danas već dobro poznate i opisane (16), a viđene su i u naših bolesnika (sl. 1-3) .

Klorokin je uz remdesivir lijek koji se najviše ispituje od početka COVID-19 pandemije. Klorokin je 4-aminokinolin koji je pokazao antivirusni učinak u SARS-CoV-1 infekciji (21). Taj se učinak temelji na nekoliko

mehanizama: povećanje endosomskog pH, inhibirajući na taj način fuziju SARS-Cov-2 virusa i stanične membrane (11); inhibicija glikozilacije angiotenzin konvertirajućeg enzimskog (ACE 2) receptora interferirajući tako s vezivanjem SARS-CoV-2 na stanični receptor (22); "u uvjetima *in vitro*" blokira transport SARS-CoV-2 iz endosoma u endolizosom, što je nužno za oslobađanje virusnog genoma (23); posjeduje imunomodulacijski učinak smanjujući produkciju proinflamatornih citokina i/ili aktivirajući anti-SARS-CoV-2 CD8 T limfocite (9).

U slučajevima progresije pneumonije u smislu sekundarne bakterijske infekcije i pogoršanja kliničkog stanja u naših je petero bolesnika korištena kombinacija teikoplanina i beta laktama (penem). Ideja je bazirana na mogućnosti teikoplanina da blokira aktivnost katepsina L (lizozomske endopeptidaze značajne u početnom procesu razgradnje proteina) i tako inhibira daljnju invaziju stanica SARS-CoV-2 virusom (slično prethodnim rezultatima u *in vitro* ispitivanjima na virusima Ebole, SARS-CoV i MERS-CoV) (24).

Jedna veća studija pokazala je da u određenog broja bolesnika (3-29 %) dolazi do brze progresije bolesti i pneumonije, nastanka ARDS-a, multiorganskog zatajivanja i smrti (3). Kako se prema iskustvu sa SARS-CoV infekcijom klinički tijek odvija u tri faze, prvoj s visokom razinom virusne replikacije i simptomima vrućice i kašlja, drugoj, nakon nekoliko dana s padom virusnog titra i simptomima pneumonije i trećoj s progresivnim padom virusnog titra ali razvojem ARDS-a u oko 20 % bolesnika, moglo se zaključiti da se radi o posljedici poremećenog imunološkog odgovora (10). Pokazalo se da u tim slučajevima dolazi do tzv. citokinske oluje i oslobađanja visokih koncentracija inflamatornih citokina kao faktora tumorske nekroze (TNF), interleukina 2, 6, 10 i brojnih drugih (4). Analize u umrlih bolesnika pokazale su velike količine citotoksičnih T limfocita i inflamatornih monocita (25). Kako je kritična komponenta u toj reakciji IL-6, već prva klinička ispitivanja u teških i kritičnih COVID-19 bolesnika tocilizumabom, humanim monoklonskim antitijelom koji blokira receptore IL-6 pokazala su mogućnost umanjivanja učinka citokinske oluje i time i smrtnosti (9,15). I u naša tri bolesnika koji su terapiju dobili u kritičnoj fazi bolesti, ali s dobrim ishodom, pokazali smo još jednu terapijsku mogućnost u odsutnosti specifičnog antivirusnog lijeka. Praćenjem koncentracije IL-6 i drugih upalnih parametara u bolesnika s progresijom bolesti za pretpostaviti je da bi ranija primjena tocilizumaba dala još bolje rezultate.

Zaključno, i klorokin i tocilizumab pokazali su u različitim fazama COVID-19 infekcije dobar učinak i mogu se preporučiti za današnje terapijske protokole.

ZAHVALA

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- Biljana Perica, sanit.ing.
- Ines Leto, mag. med. techn.

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SUMMARY

COVID-19: OUR FIRST TREATMENT EXPERIENCES

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Background: **The sudden outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) finds healthcare systems worldwide completely unprepared and all the attempts at treatment remain at the level of clinical investigations or empiric treatments, and therefore there are different treatment outcomes. Chloroquine, an old antimalarial drug and tocilizumab, the first marketed interleukin-6 blocking antibody belong to the drugs that are in use in numerous randomized clinical trials today. The aim of this report is to present our first experiences with these drugs in the treatment of COVID-19 infection.** ***Methods:*** **In the period from March 10 to May 9, 2020, 85 individuals with real-time polymerase chain reaction (RT-PCR) positive findings of SARS-CoV-2 coronavirus were registered in the Zadar County; 31 (36.5%) of them were hospitalized. Chloroquine was the initial treatment in 27 (87.1%) and a combination of lopinavir/ritonavir in three (9.6%) subjects.** ***Results:*** **Five (16.1%) patients of those treated with chloroquine were admitted to the intensive care unit because of progressive course of the disease and need for mechanical ventilation, while another three (9.6%) patients received tocilizumab, with good clinical outcome.** ***Conclusion:*** **Our results suggest the need for early inclusion of chloroquine in the treatment protocol for COVID-19 infection, and tocilizumab in the cases of severe form of the infection to prevent the disease progression.**

Key words: **SARS-CoV-2, COVID-19, chloroquine, tocilizumab, antibiotics**

Acta Med Croatica, 74 (2020) 135-144 *Review*

AGE AND SARS-COV2 INFECTION

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SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2), a novel virus of the beta coronavirus group RNA viruses, is responsible for a zoonotic disease named COVID-19 (coronavirus disease from 2019). The main receptor through which the virus enters the host cell is angiotensin-converting enzyme 2 (ACE2), known as a multifunctional protein. ACE2 expression has been found in oral and nasal mucosa, lungs, adipose tissue, heart, brain, kidneys, vascular tissue, stomach, liver. Upon entry of the virus into the target host cells, two processes are initiated, the host's immune response and the inflammatory cascade. As immune (innate and adaptive) and inflammatory responses change throughout life both qualitatively and quantitatively, both processes are responsible for varying degrees of disease severity depending on the patient's age. Short-time experience with SARS-CoV-2 infection has shown that: (i) children and adolescents develop the disease with mild symptoms, mainly on upper respiratory airways; (ii) the disease has a more severe course in adult patients with associated chronic diseases such as cardiovascular and renal diseases, chronic respiratory diseases, diabetes, etc.; and (iii) the most severe, often fatal disease occurs in the elderly, due to more pronounced processes of immunosenescence and inflamm-aging.

Key words: age, angiotensin-converting enzyme 2 (ACE2), coronaviruses, COVID-19, SARS-CoV-2

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INTRODUCTION

The beginning of 2020 was marked by the emergence of the 2019 COVID-19 pandemic (**Co**rona **Vi**rus **D**isease from 20**19**) caused by the new corona virus, SARS-CoV-2 (also known as new CoV, 2019-nCoV or COVI-19), a name derived from the syndrome name, i.e. **S**evere **A**cute **R**espiratory **S**yndrome, which first appeared in China at the end of 2019 (1) and then spread rapidly around the world. So far, the animal from which the SARS-CoV-2 was transmitted to humans is not known yet with certainty. In addition to the previously known MERS-CoV and SARS-CoV, which can cause severe clinical presentation (**M**iddle **E**ast **R**espiratory **S**yndrome and **S**evere **A**cute **R**espiratory **S**yndrome), four other human coronaviruses (229E, NL63, OC43 and HKU1) have been shown to cause infection only in the upper respiratory tract and cause relatively minor symptoms. SARS-CoV-2 has the ability to infect and actively reproduce in the upper respiratory tract.

In recent months, physicians and scientists have faced new challenges regarding COVID-19 and are focused on the investigation of a number of unknown characteristics of the novel coronavirus (its ability to infect and reproduce in the respiratory tract) (1), the receptor through which it enters human cells, the immune response and accompanying inflammation, new drugs and vaccines (2). As with other pathogens, the outcome of infection with SARS-CoV-2 depends on the amount of virus exposure at the start of infection, and on the innate and adaptive immune capabilities of the host, as well as the ability to overcome inflammation. Generally, the immune response is conditioned by age, genetic inheritance, and health condition of the host (3).

Although COVID-19 initially appeared to be a disease of the elderly and individuals whose immune system is already compromised by various chronic diseases and conditions, it was soon shown that middle-aged persons, younger persons and some children can be affected by this new viral disease.

The aim of this paper is to present literature data on the relationship between age and outcome of SARS-CoV-2 infection. In search of the review and scientific papers on the PubMed free search engine, the following key words were used: age, angiotensin-converting enzyme 2 (ACE2), coronaviruses, COVID-19, SARS-CoV-2. Articles published in English between 2003 and May 2020 were included and selected according to the relevance to the topic.

SARS-COV-2

Like other coronaviruses, SARS-CoV-2 belongs to the betaCoV group of positive-sense single-stranded RNA viruses (4, 5), diameter of approximately 60-140 nm, having four major structural proteins: the spike (S), membrane/matrix (M), small envelope (E) and nucleocapsid (N) proteins, essential to produce a structurally complete viral particle and for infection. Trimeric S glycoprotein comprises two subunits, S1 and S2 subunits. The S1 subunit contains an amino-terminal domain and a receptor-binding domain (RBD), which binds to ACE2 on the surface of epithelial cells in the lungs and other tissues. As the S glycoprotein through its RBD interacts with human ACE2 as a receptor on the target cell and mediates virus-cell fusion, it is responsible for viral entry into human cells (6). The S2 subunit comprises a fusion peptide region and two heptad repeat regions, HR1 and HR2. According to the research of other CoVs (7), the M protein defines the shape of the viral envelope, binds to the S protein and the host surface receptors, and therefore it improves membrane fusion. In addition, M protein is involved in virus replication, and is also important for virus antigenicity (8). The N protein has multiple functions: it allows virus replication, the host cellular response to viral infection, and acts as an antagonist of interferon alpha (IFN-α), a major effector cytokine in the innate antiviral response (9). The majority of E protein is localized at the site of intracellular trafficking. It seems that protein E participates in viral assembly, intracellular trafficking and pathogenesis of the virus infection (10). After SARS-CoV infection, B lymphocytes produce antibodies against these four structural proteins crucial to the development of diagnostic tests and vaccine (11).

ANGIOTENSIN-CONVERTING ENZYME 2 AND SARS-COV2 INFECTION

The monocarboxypeptidase ACE2 is a multifunctional protein that acts in several ways: (i) as an enzyme it degrades angiotensin (Ang) 2 to biologically active peptide Ang (1-7) in the renin-angiotensin system (RAS); (ii) as a receptor for SARS-CoVs, it allows the virus to penetrate the cells of various tissues (Figure 1); (iii) as an acid transporter plays an essential role in the absorption of amino acids in the kidney and gut; and (iv) in the soluble form (sACE2) present in serum, it degrades angiotensin Ang 2 to Ang (1-7) (12, 13). Although Kuba *et al.* suppose that the function of ACE2 as a SARS-CoV receptor takes place independently of its peptidase activity (12), this hypothesis needs to be proven in the future. ACE2 expression has been found in oral and nasal mucosa, lungs, adipose tissue, heart, brain, kidneys, vascular tissue, stomach, liver (13-15). Also, ACE2 is bound to peptides in circulation (both maternal and fetal), renal tubular fluid, cerebrospinal fluid, interstitial and bronchial fluid.

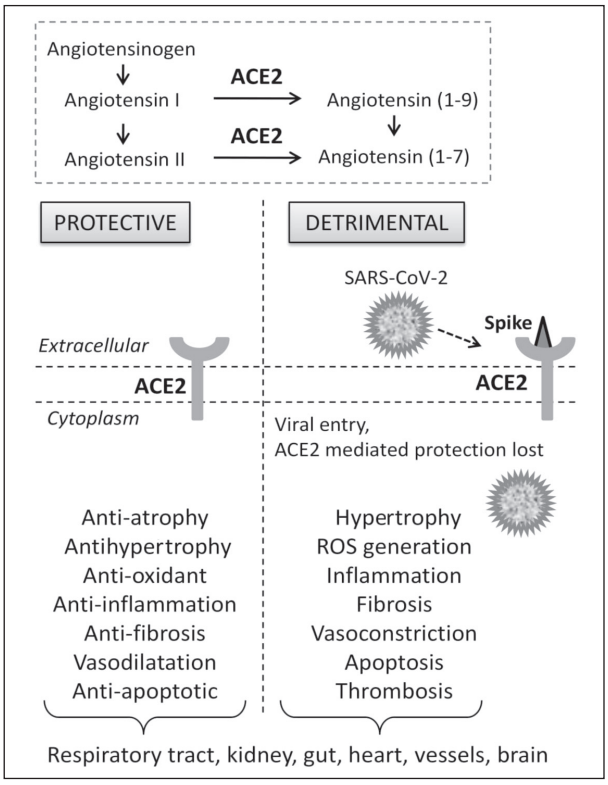

Fig. 1. *Protective effects of angiotensin-converting enzyme 2 (ACE2) and detrimental consequences after SARS-CoV-2 infection. (Adapted according to ref. 13)*

Since ACE2 was discovered, attention has been focused mainly on its function and possible roles in hypertension associated kidney and heart diseases and in pregnancy, as well as in patients with diabetes (13). However, the knowledge of ACE2 to date is still in-

sufficient to comprehend fully all aspects of the action of this enzyme, particularly regarding its role in the infection with SARS-CoV-2 and all the consequences of this infection, including the severity of COVID-19. It is located on the outer membrane of epithelial cells in the lungs (particularly in type 2 pneumocytes and macrophages) (16). The entry of SARS-CoV-2 into the cell takes place with the simultaneous activity of ACE2 and other receptors (co-receptors), such as *Mas* receptors and type II transmembrane serine protease receptor (TMPRSS2) (13, 14). SARS-CoV employs the TMPRSS2 for S protein priming. It is not yet known whether SARS-CoV-2 also employs both ACE2 and TMPRSS2 for host cell entry (17). ACE2 associated with the *Mas* receptor plays a beneficial role because it reduces inflammation and prevents development of fibrosis and pulmonary damage (13, 14). However, when SARS-CoV-2 enters cells *via* ACE2 as a receptor with consequent endocytosis, this beneficial effect will be absent and detrimental consequences will occur in the cells into which the virus has entered (Figure 1). According to the previous research on SARS-CoV infection, ACE2 has a dual function. It plays a critical role in the entry of the virus into cells, and may also be involved in post-infectious regulation (18). This post-infection regulation is supported by data that the expression of ACE2 increases 12 hours after infection, that it continues to increase significantly for 24 hours after infection, and that after 48 hours high expression still persists (19). Recently, bioinformatics methodology has enabled to identify not only ACE2 expression in the lung, but also the potential protein-protein interaction network, which regulates the network between ACE2 and inflammatory cytokines (19).

AGE-DEPENDENT EXPRESSION OF ANGIOTENSIN-CONVERTING ENZYME 2

Studies in rat lung tissues have shown that ACE2 expression in younger animals is significantly higher than in adult animals regardless of gender, and that in older animals there is a weak decrease in ACE2 expression in comparison with young and adult animals (20). These data would support the notion that ACE2 has a greater protective role, i.e. anti-atrophy, anti-oxidant, anti-inflammation, etc. in younger individuals, as presented in Figure 1. Besides, in the lungs, ACE2 expression levels and immune signature enrichment levels displayed positive correlation in older animals and negative correlation in younger animals (20). Research on ACE2 expression in lung tissue is currently limited, and is being conducted in animal tissues. To define the true role of ACE2 as a receptor for SARS-CoV-2 in children, adults and elderly patients, further research will be needed, presumably on cell cultures as well.

INNATE AND ADAPTIVE IMMUNE RESPONSE TO SARS-COV-2 VIRUS

SARS-CoV-2 first replicates rapidly in epithelial cells of respiratory and enteric system. Once the virus enters the host cells, both non-specific (cellular and humoral) and specific (cellular and humoral) (21, 22) immune mechanisms are activated, as well as the inflammatory cascade (3, 22). The first contact with the pathogen leads to the activation of the mechanisms of innate immunity, and the achievement of memory *via* memory T helper lymphocytes, in order to initiate specific immune response in re-contact with the same pathogen. This response of the adaptive immune system is particularly rapid (23).

Experience with SARS-CoV has shown that innate immunity is crucial for successful defense against the virus (24). It is not yet clear whether the immune/inflammatory response to SARS-CoV can be projected onto SARS-CoV-2, but it can be assumed that there is certain parallelism. The first reaction of the host after infection is to limit the spread of the virus in the host cells. Dendritic cells, macrophages, IFN-α, innate immune mediators, and the complement system are involved in this first phase of viral replication control (Figure 2). The proinflammatory reaction takes place simultaneously because proinflammatory cytokines are released from the infected cells, e.g., IL-6, TNF-α and IFN-β, which induce direct antiviral response and modulate other mediators of innate and adaptive immunity (such as NK cells, CD8+ lymphocytes) and the complement system (24, 25). Dendritic cells also act as antigen presenting cells, followed by the activation of naïve T lymphocytes and subsequent activation of CD4+ and CD8+ lymphocytes. CD8+ lymphocytes stimulate the synthesis of IFN-γ, which inhibits viral replication directly. CD4+ lymphocytes are aimed at stimulating the inflammatory response in the lungs (hyperinflammation). Immunohistochemical analysis of patients who died of COVID-19 revealed that deceased patients had atrophy and necrosis of the spleen and lymph node cells. In addition, lymphatic tissue macrophages contained SARS-CoV-2 nucleoprotein antigen and showed upregulation of IL-6, suggesting that macrophages may contribute to viral spread, severe inflammation, and activation-induced lymphocytic cell death during COVID-19 (26).

Upon activation, B lymphocytes are involved in the immune response by synthesizing specific immunoglobulins directed against the S and N antigens of CoV (27). Patients who manage to synthesize significant amounts of antibodies have better outcome of the infection (24).

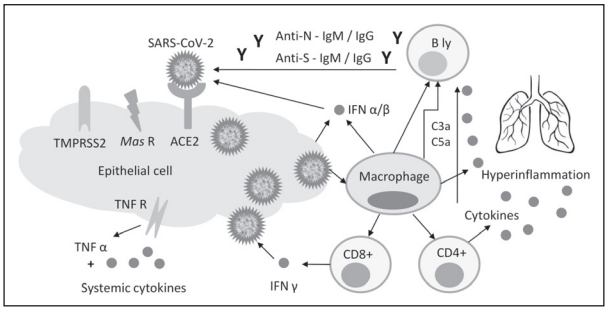

Fig. 2. *Predicted immune response and inflammation during SARS-CoV-2 infection.*

Anti-N-IgM/IgG – IgM/IgG antibodies against viral N-antigen; Anti-S-IgM/IgG – IgM/IgG antibodies against viral S-antigen; ACE2 – angiotensin converting enzyme 2; Bly – B lymphocytes; C3a – complement component 3a; C5a – complement component 5a; CD4+ – CD4+ T helper lymphocytes; CD8+ – CD8+ T helper lymphocytes; IFN – interferon; Mas R – Mas receptor; TMPRSS2 – type II transmembrane serine protease receptor; TNF α – tumor necrosis factor α; TNF R – tumor necrosis factor receptor; Y – antibody; black circle – cytokine

IMMUNITY FROM FETAL LIFE TO OLD AGE

It is generally known that the immune system develops over lifetime. At birth, the immune system is relatively immature. In general, neonatal immunity is weaker than that of adults because of tissue leukopenia, cell intrinsic hyporesponsiveness, and high values of adenosine in extracellular fluids, and inhibitory mechanisms (28). Innate immunity is considered to play a more dominant role in protecting against infection in childhood than in adulthood. The complement system represents the backbone of the innate immune system (25). In infant serum, the concentration of complement components does not exceed 80% of the value of adults, but some components may reach the value in adults already after the first month of life (28). In the first two decades, the immune system develops to a certain degree of maturity, which is maintained in adulthood, followed by a gradual decrease or weakening of physiological functions, including those of the immune system. Generally, in early adulthood, the immune system successfully maintains its balance against environmental antigens, suppresses inflammation, and heals visible and invisible damage to various tissues (Figure 3). As age advances, the immune system homeostasis becomes weaker, malignant and autoimmune diseases can occur due to environmental factors in people with genetic predisposition (28). Decline of the immune response is a consequence of impaired innate and adaptive immunity function and increasing immunosenescence, which is ultimately reflected in reduced phagocytic function, decreased number of macrophage precursors, neutrophil dysfunction, and impaired function of B and T lymphocytes (23, 28-30). In addition to immunosenescence, worsening of the clinical status of the elderly with COVID-19 is also affected by systemic chronic inflammation, known as senoinflammation (31). Due to senoinflammation, the values of proinflammatory cytokines increase in the elderly. In addition, the ability to synthesize specific antibodies decreases.

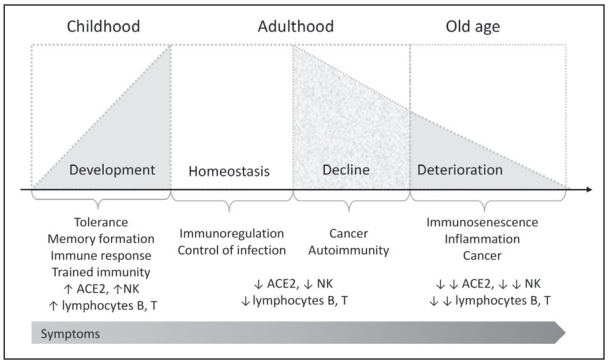

Fig. 3. *Basic features of the immune response over lifetime.*

After birth, the mechanisms of innate immunity play a major role. As the child encounters different antigens, the mechanisms of acquired immunity are increasingly emerging. In adulthood, a stable balance of the immune system and exposure to numerous antigens is established. The immune system is increasingly weakening with age, resulting in the onset of inflammation, malignant and autoimmune diseases. COVID-19 symptoms worsen with patient age. (Adapted according to ref. 22 and 28)

OUTCOMES OF SARS-COV-2 INFECTION DEPENDING ON PATIENT AGE

Short-time experience with SARS-CoV-2 infection has shown that the initial infectious dose of virus is in correlation with more severe disease (32). Children and adolescents are the healthiest segment of the entire population and generally have mild symptoms of SARS-CoV-2 infection, mainly on upper respiratory airways. If a child with SARS-CoV-2 pneumonia does not have another associated disease, COVID-19 prognosis is good (33). However, in rare cases, children may have pneumonia or multisystem inflammatory syndrome (MIS). The disease has a more severe course in patients with associated chronic diseases (cardiovascular diseases, diabetes, chronic respiratory diseases, renal disease, coagulopathy, etc.). The most severe form of the disease, often fatal, occurs in the elderly, due to more pronounced immunosenescence (3). From these observations, it can be concluded that people of good general health have milder or moderate symptoms of COVID-19, and that older people have more severe symptoms than younger patients, which can be interpreted with the functional capacity of the immune system (Figure 3). In addition, children

have higher expression of ACE2 than adults have and are less susceptible to detrimental effects of virus than older persons are. Moreover, due to low expression of ACE2, elderly patients may have more severe COVID-19 outcomes, especially those with multiple comorbidities (34, 35). Within the kidneys, ACE2 is mostly localized in tubular epithelial cells and less in glomerular epithelial cells and in renal vessels (36), where it plays a key role in the RAS. Despite the higher levels of ACE2 observed in renal epithelial cells than in lung epithelial cells, the incidence of acute kidney injury in COVID-19 is relatively low (29%), in contrast to 71% incidence of severe lung injury. Renal damage could result from pre-existing renal diseases in some adult patients, and especially older patients (37).

Recent epidemiological studies involving more than 3,000 children have shown that the majority of patients with proven SARS-CoV-2 infection were asymptomatic or had mild and moderate symptoms of COVID-19, and a 14-year-old boy died (38-40). The initial symptoms in children are fever and dry cough, and after the disease begins to worsen, rhinitis, nasal congestion, fatigue, headache, diarrhea and dyspnea can occur (41). Several reasons could affect the diagnosis of illness in children. These are less exposure of children to the source of the infection, milder symptoms of the disease, sometimes the infection goes through even without significant symptoms, thus laboratory testing for the virus is less frequently performed in children (42). Mild COVID-19 presentation in children might be associated with higher expression of ACE2 and with innate immune memory, i.e. trained immunity (immunological memory in innate immune pathways) (35). It has also been hypothesized that SARS-CoV-2 infection is less common among children than adults because of the lower maturity and function of ACE2 (38), resulting in a reduced possibility that such less functional ACE2 can bind the virus and allow it enter host cell. Differences in the immune systems between children and adults may be another reason why children respond to SARS-CoV2 infection differently from adults. Furthermore, children are more up-to-date with vaccination, which potentially may protect them from other infections due to some non-specific benefits of childhood vaccine (43).

Changes in the functional capacity of the immune system over lifetime are reflected in the values of particular immune mediators, such as absolute cell counts of B and T lymphocytes, T lymphocyte subsets in peripheral blood, as well as serum cytokine concentration (44, 45).

The number of NK cells decreases from infancy to adulthood, but in the elderly, their number gradually increases. In the elderly, the capacity of the antiviral cytokine IFN-α decreases. The percentage of T lymphocytes increases from childhood to adulthood, but decreases in the elderly. Regarding proinflammatory cytokines, the concentration of IL-1, IL-6, IL-8 and TNF-α has been shown to increase in old age in comparison to adults. At the same time, in the elderly, the concentration of Th1 cytokines (IL-2, IFN-γ) decreases, and the concentration of Th2 cytokines (IL-4, IL-10) increases (44, 45).

In the general population, about 80% of infected persons have mild signs and symptoms (tiredness, fever, cough, loss of taste and smell, headache). Other patients, i.e. those already suffering from a serious chronic illness (hypertension, diabetes, cardiovascular disease, chronic respiratory disease, and chronic renal disease) and the elderly are at a high risk of developing a severe form of the disease (acute respiratory distress syndrome (ARDS), nausea, vomiting, diarrhea) with possible lethal outcome (1, 46, 47). In individuals with impaired immunity, SARS-CoV-2 will almost undisturbed cause massive destruction of target tissues, especially in the organs with ACE2 expression, such as the lungs, intestines, and kidney. Due to inflammation damaging, pneumonia is the main cause of life-threatening respiratory disorders in the severe stage of the disease.

Elderly patients with associated diseases, such as hypertension, cardiovascular (arrhythmia) and cerebrovascular disease, chronic obstructive pulmonary disease (COPD), are at a high risk of death, with dyspnea being a key symptom (48). The main predictors of death are complications that occur in these patients, such as acute cardiac injury and cardiac insufficiency, arrhythmia, acute renal injury, ARDS, and bacterial infection.

LABORATORY FINDINGS

The aim of laboratory diagnosis in patients with SARS-CoV2 infection is to prove the presence of the virus in biological samples (nasopharyngeal and oropharyngeal swab or wash in outpatients and sputum and/or endotracheal aspirate or bronchoalveolar lavage (BAL) in inpatients), to assess the patient's general health status of target organs, immune status, and intensity of inflammation.

A. DETECTION OF SARS-COV-2

The gold standard for the detection of SARS-CoV-2 is the nucleic acid amplification testing (NAAT) by real-time polymerase chain reaction (rtPCR) and fur-

ther confirmed by next-generation sequencing (49). A positive result establishes whether the individual is currently infected with SARS-CoV-2.

B. MONITORING PATIENT HEALTH STATUS

Complete blood count (CBC), basic metabolic panel, panels for assessment of cardiac and renal function, coagulation tests, and indicators of inflammation are determined to assess the general health of the patient and screening for underlying diseases. Since children generally do not have associated diseases, changes in laboratory parameters are typical for viral infection. Children with MIS may have lymphopenia, neutrophilia, increased lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, fibrinogen, procalcitonin, D-dimer, IL-6 and decreased albumin values (50, 51). It could be assumed that otherwise healthy adults will have the same changes in laboratory findings, except for those findings that relate to changes caused by simultaneous damage to particular organs, e.g., cardiac and renal damage (Table 1) (41, 52).

Non-specific hematologic and biochemical findings depend on comorbidities and therefore on the severity of the disease (53). Accordingly, risk factors for severity of COVID-19 in adults/elderly are lymphopenia, neutrophilia, increased LDH, CRP and proinflammatory cytokines (54). It has also been established that older men who have heart damage and those with higher LDH may have an increased risk of death from COVID-19. In severe inflammatory state, inpatients may have a number of coagulation abnormalities (i.e. hypercoagulability) such as thrombocytosis, increased prothrombin time, fibrinogen, D-dimer, factor VIII (55).

Significant differences were found in laboratory findings between the dead and survivors. Longitudinal monitoring has shown that patients with worsening CBC (lymphopenia, thrombocytopenia, monocytopenia, neutrophilia), coagulation (partial thromboplastin time, D-dimer), increased biochemical parameters (aspartate aminotransferase, urea), myocardial injury markers (creatine kinase-MB, high sensitive troponin), inflammatory markers (CRP, IL-6), cellular immunity marker (CD4+), and bacterial infection marker (procalcitonin) have an increased risk of death (48).

Table 1.
Changes in common laboratory tests and their clinical significance

LABORATORY FINDING	POTENTIAL CLINICAL SIGNIFICANCE
	Detection of SARS-CoV-2
Molecular diagnostics	
SARS-CoV-2 (positive)	Confirmed SARS-CoV-2 infection
	Health assessment
Hematology	
Leukocytes, ↓↑ or↓ , [S]	Reduced immune response to the virus
Lymphocytes, ↓, [S, D]	Reduced immune response to the virus
Neutrophils, ↑ , [S, D]	Secondary bacterial infection
Monocytes, ↓, [S, D]	
MDW, ↑	Severe viral infection/viral sepsis
Platelets, ↓, [S, D]	Consumption (disseminated)/coagulopathy
Hemoglobin, ↓	Possible anemia during acute infection
Coagulation	
Prothrombin time, ↑, [S, D]	Activation of coagulation and/or disseminated coagulopathy
D-dimer, ↑, [S]	Activation of coagulation and/or disseminated coagulopathy
Biochemistry	
LDH, ↑, [S, D]	Pulmonary injury and/or multisystem damage
AST, ↑, [A] ALT↑, [S, D]	Hepatic failure and/or widespread organ damage
Bilirubin, ↑;	Hepatic failure
Fibrinogen, ↓, [A, S]	Hepatic failure
Albumin, ↓, [S]	Impaired liver function, secondary bacterial infection, septic shock
Urates, ↑, [S]	Renal injury, oxidative stress
Creatinine, urea, ↑, [A, S, D]	Renal injury
CK-MB, hs-troponin, ↑, [A, S, D]	Cardiac injury; associated with higher mortality
pro-BNP, BNP, ↑, [A]	
	Inflammation
Platelets, ↑, [S]	Inflammation, reactive thrombocytosis
Fibrinogen, ↑, [S]	Inflammation
Acute phase proteins, ↑	Acute inflammation (<6 days)
C-reactive protein, ↑, [S, D]	Viral infection; secondary bacterial infection
IL-6, IL-10, ↑, [S, D]	Proportional to the severity of inflammation
Tumor necrosis factor-α, ↑	Proportional to the severity of inflammation
Procalcitonin, ↑, [S, D]	Secondary bacterial infection and progression of the severity
Ferritin, ↑, [S]	Viral infection; secondary bacterial infection;
	Immunity status
Natural killer cells, ↓	Innate immunity; possible impaired cellular immunity
T lymphocyte subsets, ↓, [S, D]	Adaptive immunity; possible impaired cellular immunity
B lymphocytes, ↓	Adaptive immunity; possible impaired humoral immunity
Specific IgM antibodies, ↑	Indicator of (acute) contact with SARS-CoV-2
Specific IgG antibodies, ↑	Indicator of former contact with SARS-CoV-2

A – typical finding in adult/old patients; BNP – B-type natriuretic peptide; AST – aspartate aminotransferase; ALT – alanine aminotransferase; CK-MB – creatine kinase-myocardial band; hs – high sensitive; D – death risk; LDH – lactate dehydrogenase; MDW – monocyte volume distribution width; S – proportional to the severity of inflammation; SARS-CoV-2 – Severe Acute Respiratory Syndrome-CoronaVirus-2.

C. DETECTION OF ANTIBODIES AGAINST SARS-COV-2 ANTIGENS

About 10 days after the onset of symptoms, specific IgM and IgG antibodies to N, E, M and S antigens of SARS-CoV-2 can be detected in patient serum (56). The maximum value of antibodies is reached in the middle of the third week from the onset of the disease. After this time, the antibody values gradually decrease. IgM antibodies reach the lowest values about five weeks after the onset of the disease and disappear from the circulation in the seventh week after the onset of the disease. The decrease in IgG antibodies is slower and begins about seven weeks after the onset of symptoms (57). Compared to the PCR method, determination of antibodies to N antigen has the highest diagnostic sensitivity and to S antigen the greatest diagnostic specificity (56, 58).

FINAL REMARKS

At the time of writing this article, the scientific community has not reliably investigated all the characteristics of SARS-CoV-2 and the host immune and inflammatory response. Currently, there is very limited knowledge about the host immune response to SARS-CoV-2 infection. For now, conclusions on how the body copes with the virus are largely based on the knowledge about previous coronaviruses.

The virus has been shown to have the ability to infect the host, enter cells *via* ACE2, and actively reproduce in the respiratory tract and primarily cause pneumonia. Children constitute a small fraction of individuals with COVID-19, and have a milder form of the disease, probably due to higher ACE2 expression than adults, successful action of mediators of innate immunity (i.e. trained immunity) and higher number of decisive lymphocytes in the first years of life. Further research is needed to examine the true function of ACE2 in SARS-CoV-2 infection.

Most healthy adults have mild symptoms. In patients with comorbidities (hypertension, cardiovascular and cerebrovascular disease, COPD), the virus will cause more severe forms of the disease. Lymphopenia in patients with severe disease occurs mainly due to a decrease in the number of T lymphocytes. Elderly patients are at a risk of death, with worsening laboratory findings that indicate cardiac and renal damage, severe inflammation, and decreased immune function.

Explaining the mechanisms of immunosenescence and inflamm-aging may help better understand not only age-related disorders and diseases but also SARS-CoV-2 infection. Attention has been paid to determining diagnostic sensitivity, specificity and predictive value of certain biomarkers of inflammation, as well as the possible biomarkers of senescence and aging.

Determination of anti-SARS-CoV-2 antibodies (IgM and IgG classes) has no diagnostic value, but serves to assess the host's humoral response, to retrospectively assess the individual's exposure to the virus, and for epidemiological purposes. In order for the serologic test to precisely distinguish SARS-CoV-2 infection from infection with other coronaviruses, future research should examine cross-reactivity in antibody binding to specific antigens of different viruses.

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SAŽETAK

DOB I INFEKCIJA VIRUSOM SARS-COV-2

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RSARS-CoV-2 (engl. ***S**evere **A**cute **R**espiratory **S**yndrome **C**oronavirus 2*), novi virus iz skupine RNA betakoronavirusa, odgovoran je za zoonotsku bolest nazvanu COVID-19 (bolest uzrokovana koronavirusom iz 2019.). Glavni receptor pomoću kojega virus ulazi u stanicu domaćina je angiotenzin konvertirajući enzim 2 (ACE2), poznat kao multifunkcionalni protein. Receptor ACE2 prisutan je u oralnoj i nosnoj sluznici, plućima, masnom tkivu, srcu, mozgu, bubrezima, vaskularnom tkivu, želucu, jetri. Nakon ulaska virusa u ciljne stanice domaćina pokreću se dva procesa, imunosni odgovor domaćina i upalna kaskada. Budući da se imunosni (urođeni i stečeni) i upalni odgovori tijekom života mijenjaju u kvalitativnom i kvantitativnom smislu, oba procesa su odgovorna za različit stupanj ozbiljnosti bolesti, ovisno o pacijentovoj dobi. Kratkotrajno iskustvo s infekcijom uzrokovanom virusom SARS-CoV-2 pokazalo je da: (i) djeca i adolescenti razvijaju bolest s blagim simptomima, uglavnom na gornjim dišnim putevima; (ii) bolest ima teži tijek u odraslih bolesnika s pridruženim kroničnim bolestima kao što su kardiovaskularne i bubrežne bolesti, kronične respiratorne bolesti, dijabetes i sl.; (iii) najteži, često fatalni oblik pojavljuje se u starijih osoba zbog izraženijih procesa imunosenescencije i upale pri starenju.

Ključne riječi: starija dob, angiotenzin konvertirajući enzim2 (ACE2), koronavirusi, COVID-19, SARS-CoV-2

SERUM BIOMARKERS OF COLLAGEN TYPE I AND TYPE III TURNOVER IN HEART FAILURE – THE NEED FOR REAPPRAISAL

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Cardiac extracellular matrix is a complex structure presented by a network of fibrillar collagen, fibronectin, laminin, fibrillin, elastin, glycoproteins and proteoglycans. Myocardial fibrillar collagens (collagen type I and type III) are the main proteins responsible for the structural integrity of the bordering cardiomyocytes. Increased accumulation of fibrillar collagen leading to fibrosis has been reported in pathological cardiovascular conditions like heart failure. Amino-terminal and carboxy-terminal propeptides of collagen type I and III are the two major collagen types playing a central role in this process. Derived products from their turnover have been determined in serum of patients with heart failure. Collagen type I and III propeptides reflect collagen synthesis and degradation. Their use as biomarkers with prognostic or diagnostic aim is an area of intensive studies. This review article summarizes the actual available literature data on serum markers of collagen type I and III turnover in heart failure and discusses their potential as circulating indicators of cardiac fibrosis. The use of collagen type I and III peptides for diagnosis, prognosis and monitoring of heart failure is thoroughly discussed too.

Key words: collagen, biomarkers, heart failure, myocardial fibrosis

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HEART FAILURE

Heart failure (HF) is a global health problem that affects about 40 million people worldwide (1). Approximately 2% of adults have HF and in those over the age of 65, it increases to 6%-10% (2). Above 75 years of age, the rates are greater than 10% (3). Unfortunately, morbidity rate is predicted to increase because of the increased life span and risk factors such as hypertension, diabetes, dyslipidemia, and obesity (4). HF is the leading cause of hospitalization in people older than 65.

The main terminology used to describe HF is historical and based on measurement of the left ventricular ejection fraction (LVEF). HF comprises a wide range of patients, from those with normal LVEF [typically considered as ≥50%; HF with preserved EF (HFpEF)] to those with reduced LVEF [typically considered as 40%; HF with reduced EF (HFrEF)]. Patients with an LVEF in the range of 40%-49% represent a 'grey area', which the European Society of Cardiology (ESC) now defines as HFmrEF. Differentiation of patients with HF based on LVEF is important due to different underlying etiologies, demographics, comorbidities and response to therapies (5).

EXTRACELLULAR MATRIX ABNORMAL CHANGES IN HEART FAILURE

Extracellular matrix (ECM) includes a network of fibrillar collagen, basement membrane and proteoglycans. Fibrillar collagens (collagen type I and type III) ensure structural integrity of the boundary cells,

thus ensuring structural stability. ECM is a dynamic, metabolically active structure that plays an independent and important role in the progression of multiple vascular diseases. Increased accumulation of fibrillar collagen, or fibrosis, has been observed in various pathological conditions. Heart failure is a well-known example of such an adverse accumulation of ECM, raising myocardial stiffness and impairing heart contractile behavior. According to the current knowledge, the most certain collagen type I and III turnover biomarkers with clinical and laboratory value are the following four: N-terminal propeptide of collagen type I (PINP), N- terminal propeptide of collagen type III (PIIINP), C-terminal propeptide of collagen type I (PICP) and C-terminal telopeptide of collagen type I (ICTP). All of them are collagen-derived peptides as PINP and PICP reflect collagen type I synthesis, PIIINP reflects collagen type III synthesis, while ICTP shows collagen type I degradation.

It is well known that some cardiovascular diseases such as hypertension, coronary artery disease, valvular disease, and arrhythmias often progresses to HF. An association between cardiac remodeling and development of HF has been estimated (6). Cardiac remodeling is defined as a group of molecular, cellular and interstitial changes that manifest clinically as alterations in the size, mass, geometry and function of the heart after a stressful stimulus. This process can be triggered by ischemia (myocardial infarction) (7,8), inflammation (myocarditis), hemodynamic overload (workload by volume or pressure) (9) and neurohormonal activation (10,11). Cardiac remodeling is considered to be not only an adaptive event but also a maladaptive process. In result, at first stage cellular changes occur in heart structure such as myocyte hypertrophy, necrosis, apoptosis, followed by second stage of an increased ECM deposition of fibrillar collagen, often described by the term 'myocardial fibrosis'. It is associated with accelerated collagen metabolism and impaired synthesis and accumulation mainly of collagen type I and III in myocardium (12-18). In later stages of remodeling, heart function is inevitably impaired.

COLLAGEN TYPE I CHARACTERISTICS

Type I collagen is a fibrillar collagen and a major part of the interstitial membrane structure. It is the most prevalent type of collagen and a key structural composition of many tissues. It is found practically in all structures involving connective tissue. Type I collagen is the main structural protein of bone, skin, tendon, ligaments, sclera, cornea, blood vessels, as well as an important component of other tissues. It is collected in fibers forming structural-mechanical scaffold (matrix) of bones, skin, tendons, cornea, blood vessel walls, and other connective tissues. Heterotrimers of two α1 (I) and one α2 (I) chains are the dominant isoform of type I collagen. Homotrimers of three α1 (I) chains are found in fetal tissues and some fibrous lesions (19). The homotrimeric isoform is more resistant to cleavage than collagenases, which may explain its accumulation and functional role in tumors and fibrotic lesions (Fig. 1).

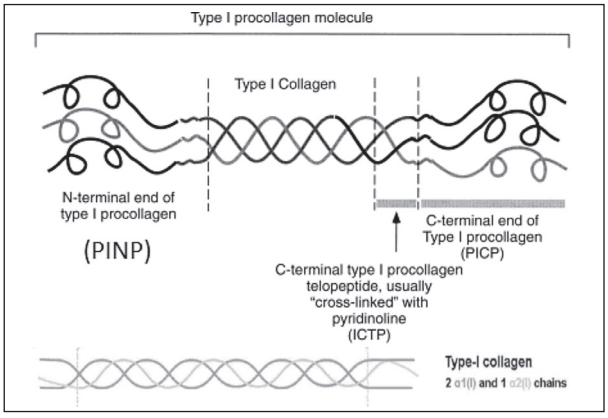

Fig. 1. *Collagen type I structure*

PICP = collagen-derived peptide including the carboxy-terminal peptide of procollagen type I formed on extracellular conversion of procollagen type I into fibrillar collagen I; PINP = collagen-derived peptide including the amino-terminal propeptide of collagen type I; ICTP = telopeptide of collagen type I. Adapted from Gao L, Orth P, Cucchiarini, M, Madry H. Effects of solid acellular type-I/III collagen biomaterials on in vitro and in vivo chondrogenesis of mesenchimal stem cells. Exp Rev Med Devices 2017; 14(9):717-32.

COLLAGEN TYPE III CHARACTERISTICS

Type III collagen is composed of one collagen α-chain, unlike most other collagens. It is a homotrimer containing three α1 (III) chains overlapped in a right triple helix. Type III collagen is secreted by fibroblasts and other types of mesenchymal cells, thus playing a major role in different inflammatory pathological conditions such as lung damage, liver diseases, renal fibrosis, and vascular fibrosis. Both collagen type III and type I are the main components of the ECM (20). Type III collagen immunological biomarkers have been developed and widely used for detection of fibrosis (Fig. 2).

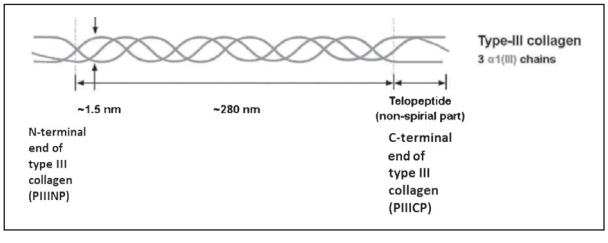

Fig. 2. *Collagen type III structure*

PIIINP = collagen-derived peptide including the amino-terminal propeptide of collagen type III arising on extracellular conversion of procollagen III to fibrillar collagen III to fibrillar collagen III. Adapted from Gao L, Orth P, Cucchiarini M, Madry H. Effects of solid acellular type-I/III collagen biomaterials on in vitro and in vivo chondrogenesis of mesenchimal stem cdells. Exp Rev Med Devices 2017; 14(9) 717-32.

CARDIAC FIBROSIS

Extracellular matrix is composed of fibrillar collagen types I and III, fibronectin, laminin, fibrillin, elastin, glycoproteins and proteoglycans; cardiac fibroblasts are the primary source of these ECM proteins. Cardiac fibroblasts also produce matrix metalloproteinases (MMPs), as well as tissue inhibitors of MMPs (TIMPs), which are ECM-regulatory proteins. MMPs are proteases that degrade ECM proteins and TIMPs can inhibit MMP function; their balanced equilibrium is critical for ECM homeostasis.

Cardiac ECM is composed predominantly of collagen type I (85%) and III (11%). Collagen type I and III are synthesized by cardiac fibroblasts. They are the main collagen-producing cells in the heart. Fibrillar collagen is synthesized firstly as a procollagen, which is split by specific proteinases in carboxy (C)- and amino (N)-terminal propeptides.

The N-terminal propeptides of collagen type I or III (PINP and PIIINP) and the C-terminal propeptides (PICP and PIIICP) are used as markers of collagen type I or III synthesis. After splitting of the propeptides, the triple helix chain will form big collagen fibers with other collagen chains. During degradation of these collagen fibers by collagenases (MMP-1, -8, -13), telopeptides are formed. The big telopeptide undergoes spontaneous denaturation in nonhelical derivatives, which are completely degraded into inactive fragments by interstitial gelatinases (MMP-2, -9). The small telopeptide of collagen type I (ICTP, 12 kDa) can be used as a marker of collagen type I degradation (21).

Accumulation of fibrillar collagen, or fibrosis, is intensified in heart failure. Early studies in the field of congestive heart failure (CHF) clearly demonstrate that extracellular degradation enzymes (MMPs) are found in the myocardium of patients with CHF (22). Evaluation of cardiac collagen metabolism by biological markers is a useful tool for monitoring cardiac tissue remodeling and fibrosis, both in laboratory models and in clinical studies (23). Along with increasing levels of collagen synthesis markers, the results reported from some studies suggest that collagen degradation is slower in patients with CHF, leading to cardiac fibrosis (19,20).

Fibrosis is a response of hyperactivity of cardiac fibroblasts that occurs in response to certain stressful stimuli. As a result, recruitment and proliferation of circulating bone marrow-derived cells infiltrate the myocardium and transform into cardiac fibroblasts. It has been reported in some studies that increased levels of collagen synthesis biomarkers (PICP, PINP, PIINCP, PIIINP) and reduced serum levels of collagen type I degradation biomarker (CITP) lead to collagen deposition and fibrosis (24-26). These data show that the balance between cardiac collagen synthesis and degradation is disturbed in pathogenic conditions (22,23). Patients with heart failure are an example of impaired collagen turnover (27,28).

CIRCULATING SERUM COLLAGEN BIOMARKERS AND HEART FAILURE

Several studies have been performed on collagen type I and III metabolism so far. They show that their turnover is mainly regulated by N-terminal propeptide of collagen type I (PINP), N- terminal propeptide of collagen type III (PIIINP), C- terminal propeptide of collagen type I (PICP) and C-terminal telopeptide of collagen type I (ICTP). They are collagen-derived peptides as PINP and PICP show collagen type I synthesis, PIIINP reflects collagen type III synthesis, while ICTP marks collagen type I degradation (25,26).

N-terminal propeptide of collagen type III (PIIINP)

PIIINP is a marker of collagen type III synthesis. Most serum PIIINP is generated during the extracellular conversion of procollagen type III to collagen type III by the enzyme procollagen aminoterminal proteinase (29). Serum PIIINP concentration correlates with the myocardial area fractions of their tissue analogs. The increase in ECM turnover, which may partially be derived from fibrosis in the myocardium, can be measured in the serum of patients with dilated cardiomyopathy, and has an impact on risk stratification and prognosis (30). In addition, reduction in the extent of collagen volume fraction in HF patients treated with spironolactone is accompanied by reductions in serum PIIINP (31) Serum PIIINP is associated with the severity (43) and outcomes of HF of different causes regardless of EF (32,33).

PIIINP levels are elevated in all HF patients regardless of EF. There is a decreased survival rate in patients with HFrEF, but the cutoff point is different, i.e. according to Zannad *et al.* (33) PIIINP >3.85 **μg**/L, in comparison with data of Klappacher *et al.* (30) PIIINP >7 **μg**/L, with clarification that patients in the latter study were all with dilated cardiomyopathy (33 idiopathic and 8 ischemic cases). Patients with HF, dilated and hypertrophic cardiomyopathy (DCM, HCM) have significantly higher serum PIIINP levels than healthy control subjects. Hypertensive patients with HFpEF also have significantly higher serum PIIINP concentrations than hypertensive patients with HFrEF and HFmrEF (31). The survival rate decreases if the

patient with HF (33,35) or with DCM (36) has an elevated PIIINP level. The serum PIIINP concentration is also significantly higher in patients with acute myocardial infarction and PIIINP >5 μg/L is an independent predictor of cardiac death and in-hospital development of CHF (37). There is only one study with patients with HFmrEF (32) which reports a decreased survival if PIIINP >4.7 μg/L (Table 1).

Table 1.
Serum levels of PIIINP in patients with heart failure

Author	Heart failure type	Main findings
Alla *et al.* (23)	HFrEF	Increased PIIINP levels
Barasch *et al.* (57)	HFrEF vs. HFpEF	Associated with HFpEF
Cicoira *et al.* (35)	HFmrEF	Decreased survival if PIIINP >4.7 **μg**/L
Martos *et al.* (34)	HFpEF	Increased PIIINP levels
Plaksej *et al.* (50)	HF	Increased levels in NYHA III + IV class
Zannad *et al.* (33)	HFrEF	Decreased survival if PIIINP >3.85 **μg**/L
Zile *et al.* (64)	HF	Increased PIIINP levels
Klappacher *et al.* (30)	DCM	Decreased survival if PIIINP >7 **μg**/L
Host *et al.* (37)	HF	Increased PIIINP levels
Schwartzkopff *et al.*(65)	HF	Independent predictors of mortality
Michalski *et al.* (67)	HFrEF *vs.* HFpEF	PIIINP showed strong negative correlation with LV-strains
MESA (Multi-Ethnic Study of Atherosclerosis) (67)	HF	Increased PIIINP levels

NYHA = New York Heart Association; DCM = dilated cardiomyopathy; HF = heart failure not defined by left ventricular ejection fraction (LVEF); HFrEF = heart failure with reduced ejection fraction (LVEF <40%); HFmrEF = heart failure with mid-range ejection fraction (LVEF 40%-49%); HFpEF = heart failure with preserved ejection fraction; (LVEF ≥50%)

N-terminal propeptide of collagen type I (PINP)

PINP is a marker of collagen type I synthesis. Procollagen type I propeptides are derived from collagen type I. This precursor contains a short signal sequence and terminal extension peptides, amino-terminal propeptide (PINP) and carboxy-terminal propeptide (PICP). These propeptide extensions are removed by specific proteinases before the collagen molecules form. Both propeptides can be found in the circulation and their concentration reflects the synthesis rate of collagen type I (38,39). In comparison with control subjects, PINP is not significantly different in patients with HCM (40), HF (41) and in hypertensive patients with or without diastolic HF (34).

C-terminal propeptide of collagen type I (PICP)

PICP is a marker of collagen type I synthesis. Serum carboxy-terminal propeptide of procollagen type I (PICP) is generated during the extracellular conversion of procollagen type I into collagen type I by the enzyme bone morphogenetic protein-1 or procollagen carboxy-terminal proteinase (42). A net release from heart into the circulation has been reported in HF (43), suggesting a cardiac origin of systemic PICP. Serum PICP concentrations correlate with collagen volume fraction (43-45) in HF. Results reported by of Lopez *et al.* (45) show that PICP levels decrease in patients with hypertensive heart failure with torasemide treatment. Serum PICP is associated with HFrEF severity (46), and with mortality in HFpEF (47) and HFrEF (48). Of interest, the serum PICP-to-serum PIIINP ratio is related to malignant ventricular arrhythmogenesis in HF (49). Data show that PICP levels are significantly increased in more studies with patients with HFpEF than HFrEF. Higher serum PICP level is found in patients with HF compared to control subjects, except for the studies by Alla *et al*. (22) and Plaksej *et al*. (50). Serum PICP, as well as coronary PICP, is positively correlated with the myocardial collagen content (51,52). There is no difference in serum PICP levels in patients with HCM (53) and DCM (54) as compared to controls. There is only one study including patients with HFmrEF, which shows that an excess of cardiac collagen type I synthesis and deposition may be involved in the enhancement of myocardial fibrosis that accompanies development of HF in hypertensive heart disease (43) (Table 2).

Table 2.
Serum levels of PICP in patients with heart failure

Author	Heart failure type	Main findings
Gonzalez *et al.* (45)	HFpEF	Increased PICP levels in both groups, patients with NYHA class II to IV CHF treated with torasemide *vs.* furosemide
Querejeta *et al.* (43)	HFmrEF	Increased PICP levels
Plaksej *et al.* (50)	HF	Non significant difference
Lopez *et al.* (51)	HHD	Strong correlation between myocardial collagen content and serum concentration of PICP
Martos *et al.* (34)	HFpEF	Increased PICP levels
Barasch *et al.* (57)	HF	Associated with HFpEF
Alla *et al.* (23)	HFrEF	Nonsignificant difference
Schwartzkopff *et al.*(65)	HFmrEF	Nonsignificant difference

NYHA = New York Heart Association; HHD = hypertensive heart disease; HF = heart failure not defined by left ventricular ejection fraction (LVEF); HFrEF = heart failure with reduced ejection fraction (LVEF <40%); HFmrEF = heart failure with mid-range ejection fraction (LVEF 40%-49%); HFpEF = heart failure with preserved ejection fraction; (LVEF ≥50%)

C-terminal telopeptide of collagen type I (ICTP)

ICTP is a marker of collagen type I degradation. Data show that ICTP levels are elevated in both groups, HFrEF and HFpEF. Increased ICTP serum levels are observed in patients with DCM and HCM too. Serum ICTP is positively related with collagen content in the myocardium (30) and it is a predictor of mortality if >7.6 μg/L (55). In hypertensive patients with HF, serum ICTP level is increased in NYHA class IV (50). Barasch *et al*. (56) did not find an association between ICTP and HFrEF and HFpEF. In patients with acute myocardial infarction, Manhenke *et al*. (57) demonstrated that ICTP was an independent predictor of total and cardiovascular mortality.

Serum collagen type I telopeptide-to-serum matrix metalloproteinase-1 ratio is a novel candidate marker studied in the last two years. As collagen cross-linking determines collagen fiber resistance to MMP degradation, the higher the cross-linking of collagen type I fibers, the lower is the cleavage of the peptide collagen type I telopeptide (CITP) by the enzyme MMP-1. Thus, the serum CITP-to-serum MMP-1 ratio is inversely correlated with myocardial collagen cross-linking (58). The CITP-to-MMP-1 ratio is independently associated with the risk of HF hospitalization (58). The combination of low CITP-to-MMP-1 ratio and high PICP identifies HF patients with the highest risk (59) (Table 3).

Table 3.
Serum levels of ICTP in patients with heart failure

Author	Heart failure type	Main findings
Plaksej *et al.* (50)	HF	Increased ICTP levels in NYHA IV
Kitahara *et al.* (55)	HFpEF	Event-free point decreases when ICTP >7.3 ng/mL
Barasch *et al.* (57)	HF	Not associated with HFpEF or HFrEF
Zile *et al.* (64)	HFpEF	Increased ICTP levels
Klappacher *et al.* (30)	DCM	Increased mortality if ICTP >7.6 μg/L
Schwartzkopff *et al.* (65)	HFmrEF	Increased ICTP levels
Batlle *et al.* (68)	HF	Increased ICTP levels and increased risk of clinical event
MESA (Multi-Ethnic Study of Atherosclerosis) (67)	HF	High levels of circulating ICTP

NYHA = New York Heart Association; DCM = dilated cardiomyopathy; HF = heart failure not defined by left ventricular ejection fraction (LVEF); HFrEF = heart failure with reduced ejection fraction (LVEF <40%); HFmrEF = heart failure with mid-range ejection fraction (LVEF 40%-49%); HFpEF = heart failure with preserved ejection fraction; (LVEF ≥50%)

CONCLUSIONS AND PERSPECTIVES

Alteration of ECM structure and function may be the key in revealing the mechanism of cardiac remodeling. Impairment of the ECM network integrity disorganizes and interrupts connections between myocardial cells and blood vessels. This could later lead to shifting of heart function. Fibrosis and overproduction of ECM proteins result in enhanced stiffness of the myocardium wall, followed by systolic and diastolic dysfunction.

The use of serum collagen-derived peptides (PINP, PICP, PIIINP and ICTP) for collagen type I and III turnover in heart failure is very promising. Potential routine clinical applications of serologic markers of collagen metabolism can hopefully be introduced soon. Despite this fact, there are some controversial findings and limitations in the studies commented here. Some important critical remarks make gaps in evidence. That is why the following questions concerning PINP, PICP, PIIINP and ICTP as indicators for diagnosis, prognosis and development of heart failure should to be taken into account:

- Changes in collagen turnover are likely to occur at a very early stage of heart failure, even before disease is clinically diagnosed. Can collagen biomarkers be used to predict development and prognosis of heart failure?
- Whether collagen metabolism markers give enough information as lone indicators, or do we need a combination model adding other cardiovascular markers, for example creatine phosphokinase, troponin? Furthermore, is it more appropriate to use an integrative model using combination of serum markers and image test than using just one of them for diagnosis, prognosis and monitoring of heart failure?
- Analyzing the above mentioned studies, some differences can be noted between the cutoff points for detection of serum levels of collagen turnover markers in HF according to the EF.
- In hypertensive patients with heart failure, serum collagen type I telopeptide-to-serum matrix metalloproteinase-1 ratio (ICTP/MMP-1) is independently associated with the risk of HF hospitalization (58). The combination of low CITP-to-MMP-1 ratio and high PICP identify HF patients with the highest risk than ICTP alone (59). Not only their absolute serum levels, but also the relationship between their serum concentration ratios could play a role in myocardial remodeling in HF. Probably the ratios between collagen marker and MMP are a more accurate indicator than a marker alone.
- The underlying factor causing the heart failure syndrome affects collagen biomarker turnover in different ways. For example, hypertension is ac-

companied by hypertrophy of cardiac myocytes and increased stiffness of the ventricle wall, which suggests an increase in collagen fibers. Patients with hypertension have thus an increase in biomarkers of the synthesis of collagen, such as PIINP and PICP.

- Different characteristics of HF patients such as HF treatment, comorbidities, age and body mass index can influence the levels of collagen biomarkers.
- Cardiac remodeling is a continuous process, while most studies were cross-sectional and report the levels of biomarkers only at one certain time point. These biomarkers should, however, be determined at various time points of the remodeling process. There is a need for larger and longitudinal investigations.
- Is a serum biomarker representative of the tissue level? A method to correlate serum levels of the biomarkers with cardiac remodeling is immunohistochemistry and histology of cardiac biopsies, which cannot be performed in cross-sectional studies. In some studies, the association between serum biomarkers and collagen content in the myocardium was investigated and serum PICP concentration was directly correlated with the fibrillar collagen fraction of the myocardium (43,52), which suggests that PICP is representative for cardiac collagen. PIIINP is also correlated with collagen type III and collagen type I, which makes PIIINP less representative for collagen type III synthesis alone (32).
- The propeptides can be incorporated in the network of collagen fibers and not cleaved off and eliminated in the circulation. At this point, PINP and PIINP underestimate partially collagen synthesis. The elimination of the peptides occurs through various pathways and is a variable process, which can affect the concentration of the biomarkers (60,61).
- Testing for circulating biomarkers of myocardial interstitial fibrosis presents several limitations. They are not thoroughly cardiac-specific, and changes in their concentrations may represent integrated abnormalities of the cardiovascular collagen and/or influence of comorbidities affecting collagen metabolism. Fibrosis also occurs in other organs and it is possible that increased levels of these biomarkers come not only from cardiac origin but also from other diseased organs such as bone, liver, kidneys and lungs. That is why in all reported studies osteoporosis, renal failure and hepatic fibrosis were used as exclusion criteria (62).
- In most of the studies, patients were obviously treated with standard HF pharmacotherapy. However, does the drug treatment affect the elimination of these propeptides by liver and kidneys and does it interfere with the dynamic processes in cardiac extracellular matrix?

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SAŽETAK

SERUMSKI BIOMARKERI PRETVORBE KOLAGENA I I III. KOD ZATAJENJA SRCA – POTREBA PONOVNE PROCJENE

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Ekstracelularni matriks srca je složena struktura koja se prikazuje kao mreža vlaknatog kolagena, fibronektina, laminina, fibrilina, elastina, glikoproteina i proteoglikana. Vlaknati kolageni miokarda (kolagen tipa I. i tipa III.) su glavni proteini o kojima ovisi strukturni integritet graničnih kardiomiocita. Povećano nakupljanje vlaknatih kolagena koje dovodi do fibroze opisano je u patološkim kardiovaskularnim stanjima kao što je zatajenje srca. Amino-terminalni i karboksi-terminalni propeptidi kolagena tipa I. i III. dva su glavna tipa kolagena koji imaju središnju ulogu u tom procesu. Produkti njihove pretvorbe određivani su u serumu bolesnika sa zatajenjem srca. Propetidi kolagena tipa I. i III. odražavaju sintezu i raspad kolagena. Njihova upotreba kao biomarkera područje je intenzivnih studija sa svrhom prognoze ili dijagnoze. Ovaj pregledni rad sažima danas raspoložive podatke iz literature o biljezima pretvorbe kolagena tipa I. i III. kod zatajenja srca i raspravlja se o njihovom potencijalu kao cirkulirajućim pokazateljima fibroze srca. Raspravlja se i o primjeni peptida kolagena tipa I. i III. za dijagnozu, prognozu i praćenje zatajenja srca.

Ključne riječi: **kolagen, biomarkeri, zatajenje srca, fibroza miokarda**

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LIJEČENJE MULTIPLE SKLEROZE LIJEKOM KLADRIBIN – RETROSPEKTIVNA JEDNOGODIŠNJA ANALIZA U KLINICI ZA NEUROLOGIJU KLINIČKOG BOLNIČKOG CENTRA SESTRE MILOSRDNICE U ZAGREBU

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Kladribin (Mavenclad®, Merck, Nizozemska) je lijek koji se primjenjuje u liječenju visoko aktivnog oblika multiple skleroze (MS). Mehanizam djelovanja nije u potpunosti jasan, ali se smatra da lijek djeluje na funkciju DNA i mitohondrija čime dovodi do apopoptoze limfocita. Djelotvornost i sigurnost kladribina bile su procijenjene u randomiziranom, dvostruko slijepom, placebom kontroliranom kliničkom ispitivanju (studija CLARITY) te kasnijim istraživanjima koja su proizašla iz tog ispitivanja. U navedenom ispitivanju bolesnici s relapsno remitentnom multiplom sklerozom (RRMS) liječeni kladribinom pokazali su statistički značajno poboljšanje u godišnjoj stopi relapsa, udjelu bolesnika bez relapsa i udjelu bolesnika bez postojane onesposobljenosti. Cilj ovog rada bio je analizirati bolesnike s MS-om koji su liječeni kladribinom na Klinici za neurologiju Kliničkog bolničkog centra Sestre milosrdnice u Zagrebu te usporediti rezultate s postojećim saznanjima o lijeku. Retrospektivnom analizom u godini dana analizirali smo bolesnike kod kojih je bilo indicirano liječenje kladribinom. Ukupno je kladribin primijenjen 15-orici bolesnika. Od toga je 46 % bolesnika prethodno bilo liječeno imunomodulacijskom terapijom prve linije, a 53 % bolesnika nije bilo liječeno takvom terapijom. Nakon godine dana, prije primjene drugog ciklusa lijeka, za vrijeme pisanja ovog rada, kod 66 % bolesnika nije bilo relapsa. Ukupno je bilo 20 % nuspojava od kojih su najčešće bile kožne reakcije. Analizom naše skupine bolesnika određen dio rezultata odgovarao je rezultatima studije CLARITY, a ostali podatci bili su približni rezultatima navedenog ispitivanja. Također, primjena lijeka protekla je uz manji dio nuspojava. Ipak, za detaljniju analizu potreban je veći broj bolesnika te se u budućnosti planiraju prikazati i navedeni podatci.

Ključne riječi: multipla skleroza, kladribin, liječenje, iskustva

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UVOD

Kladribin (Mavenclad®, Merck, Nizozemska) je lijek koji je indiciran u liječenju bolesnika s visoko aktivnim oblikom relapsno remitentne multiple skleroze (RRMS). Mehanizam djelovanja lijeka nije u potpunosti razjašnjen, ali se smatra da djeluje na funkciju DNA i mitohondrija čime dovodi do apopoptoze limfocita (1). Indikacije i kriteriji Hrvatskog neurološkog društva za primjenu kladribina navedene su u tablici 1 (2). Djelotvornost i sigurnost kladribina bile su procijenjene u randomiziranom, dvostruko slijepom, placebom kontroliranom kliničkom ispitivanju (studija CLARITY). Bolesnici s RRMS-om koji su primili kladribin u dozi od 3,5 mg/kg pokazali su statistički značajno poboljšanje u godišnjoj stopi relapsa, udjelu bolesnika bez relapsa, udjelu bolesnika bez postojane onesposobljenosti tijekom 96 tjedana i vremenu do 3-mjesečne progresije mjerene ljestvicom EDSS (*Extended Disability Status Scale*). Također, bolesnici liječeni kladribinom pokazali su relativno smanjenje broja T1 gadolinij pozitivnih (Gd+) lezija, aktivnih

T2 lezija i kombiniranih jedinstvenih lezija na (MR) magnetskoj rezonanci mozga i vratne kralježnice. Naknadna analiza pokazala je 47 % smanjenje rizika od progresije (3,4). S obzirom da lijek djeluje na smanjenje limfocita važno je pratiti razinu limfocita prije početka liječenja u prvoj godini liječenja, prije započinjanja liječenja u drugoj godini liječenja te dva do šest mjeseci nakon početka liječenja u svakoj godini liječenja. Lijek je kontraindiciran u stanjima postojeće imunosupresije, aktivne kronične infekcije (tuberkuloza, hepatitis), aktivne infekcije virusom humane imunodeficijencije (HIV), aktivne zloćudne bolesti, umjerenog ili teškog oštećenja bubrega te u trudnoći (1).

Tablica 1.

Kriteriji za početak liječenja imunomodulacijskom terapijom druge linije kod liječenja bolesnika sa RRMS prema smjernicama Hrvatskog neurološkog društva.

Indikacije za početak liječenja drugom linijom terapije (natalizumabom /fingolimodom / alemtuzumabom/ kladribinom / okrelizumabom) kod bolesnika s relapsno-remitirajućom multiplom sklerozom:
1. Bolesnici kod kojih je bolest aktivna unatoč prvoj liniji terapije: a. ≥4 nove T2 lezije na MR-u nakon početka liječenja lijekovima prve linije ili b. ≥2 relapsa nakon početka liječenja lijekovima prve linije 2. EDSS ≤ 7,0 3. Odsutnost trudnoće 4. Odobrenje bolničkog povjerenstva za lijekove
Jedan lijek druge linije terapije u drugi lijek druge linije terapije (natalizumab /fingolimod / alemtuzumab/ kladribin / okrelizumab) u bolesnika s relapsno-remitirajućom multiplom sklerozom se može promijeniti na indikaciju nadležnog neurologa, a u slučaju:
1. ≥1 relapsa nakon početka liječenja lijekovima druge linije 2. Nepodnošljivih nuspojava liječenja 3. U bolesnika liječenih natalizumabom u slučaju visokog titra anti JCV protutijela te povišenog rizika razvoja progresivne multifokalne leukoencefalopatije (PML)
Indikacije za početak liječenja bolesnika s brzonapredujućom multiplom sklerozom (natalizumabom / fingolimodom / alemtuzumabom/ kladribinom / okrelizumabom)
1. Bolesnici s teškom brzo napredujućom relapsno-remitirajućom multiplom sklerozom definiranom s 2 ili više onesposobljavajućih relapsa (motorički relaps, ataksija, moždano deblo) u trajanju manje od jedne godine neovisno o trajanju bolesti i prethodnoj terapiji 2. EDSS ≤ 7,0 3. Odsutnost trudnoće 4. Odobrenje bolničkog povjerenstva za lijekove

(Preuzeto i modificirano prema: Smjernice Hrvatskog neurološkog društva za liječenje multiple skleroze. Dostupno na: https://neuro-hr.org/Content/Documents/Kriteriji-za-lijecenje-RRMS-a-2018-002.pdf).

CILJ

Cilj ovograda bio je retrospektivno, u razdoblju od jedne godine, prikazati skupinu bolesnika s RRMS-om koja je liječena kladribinom na Klinici za neurologiju Kliničkog bolničkog centra Sestre milosrdnice te usporediti pokazatelje praćenja sa studijom CLARITY i postojećim saznanjima o lijeku.

METODE

Na Klinici za neurologiju Kliničkog bolničkog centra Sestre milosrdnice kladribin je prvi put primijenjen u rujnu 2018. godine. Lijek je davan u dozi 3,5 mg/kg prema individualnoj tjelesnoj težini bolesnika prema odgovarajućoj shemi doze po danu. Obrada prije primjene lijeka uključivala je: kompletnu krvnu sliku (KKS), diferencijalnu krvnu sliku (DKS), enzime jetrene funkcije, sediment urina, testiranje na hepatitis B i C, test na John Cunningham virus (JCV), testove na virus varičela zoster (VZV), kvantiferonski test, HIV test, MR mozga i vratne kralježnice. Pokazatelji koje smo pratili uključivali su: dob, spol, prosječno vrijeme od pojave simptoma do početka liječenja kladribinom, prosječno vrijeme od pojave dijagnoze do početka liječenja kladribinom, prosječan EDSS prije početka primjene lijeka, vrsta imunomodulatorne terapije prije primjene kladribina, broj relapsa u godini dana prije primjene lijeka, broj novih i gadolinij imbibirajućih lezija na MR-u mozga i vratne kralježnice prije primjene kladribina, radiološki ishod na MR-u nakon primjene kladribina, klinički ishod nakon primjene kladribina, broj limfocita prije početne primjene lijeka, broj limfocita nakon dva i šest mjeseci nakon primjene lijeka te vrste nuspojava.

REZULTATI

Od rujna 2018. do listopada 2019. godine kladribin je primijenjen kod ukupno 15 bolesnika. Od toga su kod 13 bolesnika (86 %) provedena dva ciklusa liječenja. Prosječna dob bolesnika bila je 38,93 godina. Lijek je primijenjen kod 66 % žena i kod 33 % muškaraca. Prosječno vrijeme od pojave simptoma bilo je 8,53 godine, a od postavljanja dijagnoze 6,85 godina. Prethodno je kod 46 % bolesnika primijenjena imunomodulacijska terapija prve linije, a kod 53 % bolesnika kladribin je bio lijek prvog izbora zbog visoke aktivnosti bolesti. Prosječan EDSS prije primjene lijeka bio je 2,8. Dvadeset i šest posto bolesnika je na prethodnoj MR snimci mozga i vratne kralježnice pokazalo gadolinij imbibirajuće lezije, a prosječan broj gadolinij imbibirajućih lezija bio je 1,06. Kod 73 % bolesnika došlo je do pojave novih lezija (prosječan broj novih lezija 2,27). Što se tiče kliničkog ishoda nakon primjene prvog ciklusa lijeka kod 46 % bolesnika nastupilo je poboljšanje, kod 20 % stanje je bilo bez promjene, a kod 6 % bolesnika došlo je do pogoršanja (tablica 2). Od nuspojava najčešće su bile prisutne kožne reakcije (urtikarija) (tablica 3).

Tablica 2.
Rezultati jednogodišnje analize bolesnika kod kojih je primijenjen kladribin. (Rezultati su izraženi brojem (n), postotcima (%) i standardnom devijacijom (±)).

Prosječna dob	**38,93 (±8,35)**
Spol (n, %)	
• Žene • Muškarci	10/15 (66) 5/15 (33)
Prosječno vrijeme od pojave simptoma (godine)	8,53 (±7,45)
Prosječno vrijeme od postavljanja dijagnoze	6,85 (±7,58)
Prosječan EDSS prije početka primjene kladribina (n, %)	2,8 (±1,65)
• 0 • 1 • 1,5 • 2 • 2,5 • 3 • 3,5 • 4 • 4,5 • ≥5	1 (6) 3 (20) 0 3 (20) 1 (6) 1 (6) 2 (13) 0 2 (13) 2 (13)
Broj bolesnika kod kojih je prethodno primijenjena imunomodulacijska terapija (n, %) *	7/15 (46)
• Interferon • Glatiramer acetat • Dimetil fumarat • Terinoflumid	2/15 (13) 4/15 (26) 1/15 (6) 1/15 (6)
Broj bolesnika bez prethodne imunomodulacijske terapije (n, %)	8/15 (53)
Prosječan broj relapsa u godini prije primjene kladribina	1,87 (±0,62)
Broj bolesnika s novim lezijama prije primjene kladribina (n, %)	11/15 (73)
• Prosječan broj novih lezija prije primjene kladribina	2,27 (±3,64)
Broj bolesnika s gadolinijem imbibirajućim lezijama prije primjene kladribina (n, %)	4/16 (26)
• Prosječan broj gadolinijem imbibirajućih lezija prije primjene kladribina • Prosječan broj gadolinijem imbibirajućih lezija nakon primjene kladribina	1,06 (±2,56) 1 (±1)
Broj bolesnika kod kojih je proveden drugi ciklus (n, %)	13/15 (86)
Klinički ishod prije primjene drugog ciklusa	
• poboljšanje • stacionarno • pogoršanje	7/15 (46) 3/15 (20) 1/15 (6)
Godišnja stopa relapsa	0,06 (±0,25), p=0,0

*kod jednog bolesnika primijenjena su dva lijeka prve linije

Tablica 3.
Prikaz nuspojava bolesnika liječenih kladribinom. (Rezultati su izraženi izraženi brojem (n), postotcima (%) i standardnom devijacijom (±)).

Nuspojave Prosječan broj svih nuspojava (n, %)	n 3/15 (20)
• Infekcije - herpes simpleks	1/15 (6)
• Kožne reakcije – urtike	2/15 (13)
• Ostalo	0
• Prosječan broj limfocita prije primjene kladribina (10^9/L)	1,96 (±0,99)
• Prosječan broj limfocita nakon 2 mjeseca	1,28 (±0,54)
• Prosječan broj limfocita nakon 6 mjeseci	1,20 (±0,49)

RASPRAVA

Naše rezultate odlučili smo usporediti s rezultatima studije CLARITY kod skupine bolesnika koja je liječena kladribinom u istoj dozi kao i naši bolesnici. Analizom naših bolesnika utvrdili smo da je prosječna dob bila 38,93 godine što je nešto veća dob u odnosu na prosječnu dob bolesnika u studiji CLARITY u kojoj je prosječna dob bila 37,9 godina. Što se spolne distribucije tiče, analizom naše skupine bolesnika utvrdili smo da ima ukupno 66 % žena, što također odgovara rezultatima studije CLARITY gdje je bilo ukupno 68,8% žena. Prosječno vrijeme od pojave simptoma bilo je 8,3 godine, a u studiji CLARITY 7,9 godina. Što se prethodne imunomodulacijske terapije tiče, kod 46 % bolesnika provedeno je prethodno liječenje imunomodulacijskom terapijom prve linije, dok je u studiji CLARITY kod 26 % provedeno prethodno liječenje imunomodulacijskom terapijom. Također, kod jednog od naših bolesnika prethodno je provedeno liječenje s dva lijeka prve linije. Prosječan EDSS kod naše skupine bolesnika bio je 2,8 kao i u studiji CLARITY što ukazuje u prilog da smo dobro izabrali skupinu bolesnika kod koje je bilo potrebno primijeniti ovaj lijek. U našoj skupini 26 % bolesnika pokazalo je gadolinij imbibirajuće lezije na ranijoj MR snimci dok je prosječan broj lezija bio 1,06. U studiji CLARITY broj gadolinij imbibirajućih lezija bio je nešto viši kod 31,9 % bolesnika, a prosječan broj lezija bio je 1,0. Kod 73 % naših bolesnika došlo je i do pojave novih lezija prije liječenja kladribinom što također ukazuje na aktivnost osnovne bolesti tako da smo u podatke praćenja uključili i ovaj pokazatelj. Do sada, što se kliničkog ishoda tiče, kod jedne bolesnice (6 %) došlo je do pojave jednog relapsa, i to 20 tjedana nakon prve primjene lijeka. U studiji CLARITY do pojave relapsa došlo je u nešto većem postotku (15,9 %), ali nakon 96 tjedana praćenja. Kod 66 % naših bolesnika klinički ishod bio je bez promjene ili poboljšanja stanja, što je relativno niže u odnosu na ispitivanje CLARITY koje je proma-

tralo pokazatelj bolesnika bez relapsa čiji je postotak bio je 79,7 %. Rezultati studije CLARITY pokazali su smanjenje broja broja novih gadolinij imbibirajućih lezija nakon 96 tjedana (prosječan broj 0,13). Zbog retrospektivne analize, a s obzirom na ograničenost dostupnih MR snimki u sustavu, naši rezultati prikazali su u prosjeku jednu leziju, što je nešto manje u odnosu na MR nalaz prije primjene lijeka (prosječno 1,06 lezija). Trenutno je potreban veći broj snimki za detaljniju analizu ovog pokazatelja. Što se godišnje stope relapsa tiče u studiji CLARITY ona je iznosila 0,14, a u našem slučaju 0,06 što je manje, ali povećanjem broja bolesnika navedeni će podatci biti bolje prikazani. Što se tiče nuspojava, zabilježen je relativno nešto niži postotak (20 %) u odnosu na studiju CLARITY. U ispitivanju CLARITY zabilježeno je 80 % nuspojava. Najčešće nuspojave bile su glavobolja i limfopenija. U našoj skupini bolesnika najčešće su bile urtikarije (13 %). Kod jedne bolesnice zbog opsežne urtikarije i moguće alergijske reakcije na lijek odlučeno je primijeniti lijek u sljedećoj dozi uz individualnu procjenu doze kliničkog farmakologa. Što se limfopenije tiče kod naših je bolesnika primijećeno opadanje vrijednosti limfocita, ali još uvijek se nije radilo o limfopeniji trećeg i četvrtog stupnja.

ZAKLJUČAK

Naši rezultati liječenja kladribinom su u odnosu na studiju CLARITY zadovoljavajući. Najviše smo zadovoljni smanjenjem relapsa i smanjenjem progresije bolesti te relativno malim brojem nuspojava. Također, odlučili smo u daljnje praćenje uključiti i same bolesnike s ciljem da se jave nadležnom neurologu u slučaju sumnje na određenu nuspojavu. Daljnjim praćenjem planiramo detaljno pratiti bolesnike i dobivene rezultate usporediti sa studijom CLARITY.

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SUMMARY

TREATMENT OF MULTIPLE SCLEROSIS WITH CLADRIBINE – A RETROSPECTIVE ONE-YEAR ANALYSIS AT DEPARTMENT OF NEUROLOGY, SESTRE MILOSRDNICE UNIVERSITY HOSPITAL CENTRE IN ZAGREB

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Cladribine (Mavenclad®, Merck Europe, The Netherlands) is a drug used in patients with highly active multiple sclerosis (MS). The exact mechanism is not known but it is considered that drug affects the function of DNA and mitochondria leading to apoptosis of lymphocytes. The efficacy and safety of cladribine were evaluated in a randomized, double-blind, placebo-controlled clinical trial (CLARITY study) and later on in studies resulting from this study. Patients with relapsing-remitting MS (RRMS) who received cladribine had a statistically significant improvement in the annual rate of relapse, proportion of relapse-free patients and proportion of patients without persistent disability. The aim of this study was to analyze MS patients treated with cladribine at the Department of Neurology, Sestre milosrdnice University Hospital Centre and to compare the results with the existing findings on the drug. This retrospective one-year analysis included patients eligible for cladribine treatment. In total, cladribine was administered to 15 patients. Of these, 46% of patients had previously received first-line immunomodulatory therapy and 53% of patients had not previously undergone immunomodulatory therapy. After one year, before applying second drug cycle, there were no relapses in 66% of patients. In total, there were 20% of side effects, mostly skin reactions. Analysis of data on our group of patients revealed that some of the results were consistent with the CLARITY study, and certain data were approximate to this study. Also, drug administration was associated with a small proportion of side effects. However, additional analysis in a greater patient sample is required, and we plan to extend this study and provide new information in the future.

Key words: multiple sclerosis, cladribine, treatment, experience

PREGNANCY – MISSED PREVENTION AND INTERVENTION OPPORTUNITIES IN COMMUNITY HEALTH NURSING

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Attachment is a term used to describe a deep and lasting emotional relationship with another individual. It primarily designates emotion between a mother and her baby, but it is also inherent to life-long human behavior. It is characterized by a tendency to seek and maintain closeness with caring people in stressful situations. The feeling of safety that is generated through the mother-child relationship is the foundation for basic trust or distrust in relationships, and also affects children's expectations concerning how the environment will respond to their needs. Development of attachment is to a large extent determined by the mother's responsiveness to the child's needs, compatibility of the mother and her child, the child's temperament, the mother's recollections of her childhood, and the supporting community. Good functioning of families is of great importance to all family members, especially pregnant women. The health care system supports pregnant women through the visiting nurse service that is in charge of preventive measures. Of all health professionals, the community health nurse is the only one who, visiting the home and family environment of a pregnant woman, has complete insight into the possible occurrence of risk factors for the development of maternal and child disorders. With this intervention, we can act preventively in order to preserve physical, mental and social well-being. The aim of this study was to determine discrepancy in the number of anticipated and performed preventive nursing visits to pregnant women in Croatia. The situation was analyzed at county (regional) and national level. The authors used the information on the health care of pregnant women, puerperal women and infants up to 12 months of age published in the Croatian Health Statistics Yearbooks and in reports on the natural change in the population by the Croatian Bureau of Statistics between 1995 and 2018. Study results showed the rate of nursing visits to pregnant women and to infants up to 12 months of age, as well as the difference in the number of nursing visits in the Republic of Croatia over a period of 23 years. During the observed period, there was a significant drop in the total number of childbirths, as well as in the number of nursing visits to pregnant women, and the trend has continued. During the observed period, a mean of 42.1% of women went through their pregnancy without a single nursing visit, which means that an opportunity to provide such a vulnerable group with an important segment of social and professional support was lost. The potential opened by drop in the number of pregnant women to increase the scope of nursing visits to at least once per pregnancy, after the 16th week of pregnancy, remained unused. The number of visits to newborns and women in the puerperal period was on the rise, while visits to infants were oscillating with a slight downward trend. In conclusion, the opportunity created by drop in the number of pregnancies was not utilized to improve the scope of community nurse visits to at least once in pregnancy after week 16. Community health nursing for pregnant women failed to reach the desired health care standard.

Key words: visiting nurse, pregnant women, health care organization, Croatia

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INTRODUCTION

Good functioning of families is of great importance to all family members, especially pregnant women. The health care system supports pregnant women through the visiting nurse service that is in charge of implementing preventive measures. Of all health professionals, the community health nurse is the only one who, visiting the home and family environment of a pregnant woman, has complete insight into the

possible occurrence of risk factors for development of maternal and child disorders. With this intervention, we can act preventively in order to preserve physical, mental and social well-being.

Immediately after giving birth, a sensitive phase for the mother, the newborn and the father begins; one that is going to have a major impact on the relationship that is later to be developed between the parents and their children. During the first few hours of life, the newborn is basically accepted and the mother-child bond is created. Uninterrupted contact with the parents, primarily between the mother and the child, immediately after birth, has positive impact on the psychological development of the child and his/her social behavior. Bonding designates strong emotional link that is developed between the mother and her baby at childbirth (1). Bonding is continuation of the connection that started developing during pregnancy. Physical and chemical changes that occurred in the pregnant woman's body reminded the mother-to-be of the presence of a new individual. Birth makes this connection stronger and 'real', while bonding enables channeling of love to the baby. From the moment they are born, children learn about the world around them by observing their parents. Parents are the child's most important teachers. The baby's first experiences in interaction with his/her parents leave an impact on his/her overall growth and development. The first senses that babies rely on are touch and smell, which is why skin-to-skin contact and breastfeeding are extremely important for both the baby and the mother. Improving initial contacts will improve communication, and thus humanization (2).

The need for attachment is a fundamental human need. When displaying attachment behavior, the child's main objective is to be near the person that makes him/her feel safe. Attachment development towards a mother or primary care giver is a process that starts shortly after birth and can be clearly identified in six- to eight-month-old infants (3). It is a universal pattern in human development, manifested differently among various cultures (4). Children use attached behavior to increase closeness to a potential caregiver and to encourage positive reactions, increasing the likelihood of getting help for a weak, dependent or threatened child. Such behavior serves as a guarantee that a 'safe base' will be found in the form of a reliable individual whose love and attention they can rely on, before going on to discover the wider environment. Attachment is crucial for the child's well-being and his/her future development (5).

There are four main functions to attachment, i.e. it provides a sense of safety and security, regulates affect and excitement, promotes emotional expression and communication, and serves as grounds for research. In the process, emotions act like signals. The presence of the mother is psychologically as important for the child as the mother's milk (6). During the first several weeks of life, the baby is learning about his/her mother's characteristics. Repetitive interactions help it recognize his/her mother by her face, smile, touch and voice. Attachment styles are to a significant degree determined by the quality of care given to the newborn. The mother's sensitivity to the child's needs, how quickly and adequately the baby's needs are met, pampering and encouragement, all of these provide emotional safety and stimulation, which are so important for normal development (7). In this manner, the mother's bonding with her newborn immediately after birth eventually leads to good attachment.

Emotional warmth is especially important for human development as emotions are the language of socialization. Development of attachment is to a large extent determined by the mother's responsiveness to the child's needs, the compatibility of the mother and her child, the child's temperament, the mother's recollections of her childhood, and the supporting community (2). Any one of the elements that have an impact on the early mother-child relationship can also be a disturbing factor and lead to development of an insecure (anxious) attachment style (2).

New mothers can be given informal support, wider social support, professional care, but also support provided by the family and the partner. Informational support refers to providing the new mother with advice and guidance. Instrumental support is any tangible form of assistance given to new mothers, such as material aid or assistance with tasks. Emotional support can be provided by expressions of care, empathy and esteem for new mothers (8).

Well-functioning families and well-developed family relationships are some of the most important components of social support, which can take the form of emotional or instrumental support. Being able to efficiently address cultural, ecologic, psychosocial and socio-economic stresses throughout the family's life cycle is what defines well-functioning families. It is characterized by the ability of the family system to satisfy the needs of its members throughout its developmental stages (Nursing Outcomes Classification, NOC) (9).

According to the current program of measures, the visiting nurse service in the Republic of Croatia should implement one community nurse visit *per* pregnancy, two visits to puerperal women and newborns, two visits to newborns, one to preschool children, and at least one visit to other children or the school (10,11). These

are the foreseen standards, but implementation usually comes short of the set standards, which means that the opportunity to implement preventive measures and contribute to the health of future generations is being missed (12-14).

METHODS

The number of nursing visits during pregnancy was analyzed as a possible indicator of successful interventions and compared with the total number of childbirths. The number of pregnant women who were not visited at least once by community nurses while pregnant was also calculated for each county (region) of the Republic of Croatia and for the whole country. Data published in the Croatian Health Statistics Yearbooks and in reports on the natural population change by the Croatian Bureau of Statistics between 1995 and 2018 were analyzed and are shown in tables and figures (15,16).

RESULTS

This study searched data on the medical intervention that has a great potential to influence nursing outcomes, but which has been unduly neglected in most local communities in the Republic of Croatia, i.e. community nurse visits to pregnant women after the 16th week of pregnancy. The authors compared the rate of nursing visits to pregnant women at county level and provide a view on the current trends at the national level during the period of observation.

Table 1.
Number of visits to pregnant women, childbirths and pregnant women who did not receive nursing visit in 2018, according to counties of the Republic of Croatia

County	Visits to pregnant women (1 *per* pregnancy)	Childbirths total	Pregnant women with no nursing visits during pregnancy	% of all pregnant women without a single nursing visit during pregnancy
City of Zagreb	2401	8269	5868	71.3
Zagreb County	836	2762	1926	69.9
Krapina-Zagorje	713	1116	403	36.1
Sisak-Moslavina	208	1229	1021	83.1
Karlovac	124	963	839	87.2
Varaždin	586	1441	855	59.3
Koprivnica-Križevci	361	1005	644	64.1
Bjelovar-Bilogora	787	994	207	20.8
Primorje-Gorski Kotar	2442	2137	0	0.0
Lika-Senj	202	367	165	45.0
Virovitica-Podravina	283	695	412	59.3
Požega-Slavonia	163	600	437	72.8
Brod-Posavina	577	1198	621	51.8
Zadar	113	1546	1433	92.7
Osijek-Baranja	1022	2353	1331	56.6
Šibenik-Knin	35	800	765	95.6
Vukovar-Srijem	944	1283	339	26.4
Split-Dalmatia	829	4287	3458	80.7
Istria	514	1676	1162	69.3
Dubrovnik-Neretva	450	1196	746	62.4
Međimurje	479	1192	713	59.8
Overall	14,070	37,109	23,345	61.2

Table 1 shows data on the number of nursing visits to pregnant women, total number of childbirths and number of pregnant women who did not receive nursing visit during pregnancy, for each county and overall for the Republic of Croatia. During 2018, a total of 37,109 babies were born in Croatia and there were 14,070 nursing visits to pregnant women. This implies that 23,345 (61.18%) women went through their pregnancy without a single nursing visit, which means that an opportunity to provide such a vulnerable group with an important segment of social and professional support was lost. The worst ranking, with more than 70% of pregnant women who did not receive nursing visit, was the Šibenik-Knin County (95.6%), followed by the Zadar (92.7), Split-Dalmatia (80.7%), Karlovac (87.2%), Sisak-Moslavina (83.1%), Požega-Slavonia (72.8%) counties and the City of Zagreb (71.3%) (Table 1). Compared with the total number of births, nursing visits were rather rare and there were many women who had not received a single visit of community nurses. Data shown here reflect the situation at the country level, while regional data are displayed in Table 1.

The numbers differ, indicating that the approach to this issue varies countrywide. The Primorje-Gorski Kotar County was leading in the number of nursing visits to pregnant women, while in the Zadar and Split-Dalmatia Counties and the City of Zagreb nursing visits were organized almost solely for high-risk pregnancies.

Table 2.
Nursing visits to pregnant women and babies and difference in the number of visits in the Republic of Croatia between 1995 and 2018

Year	Childbirths total	Nursing visits to pregnant women	Difference in childbirth total and nursing visits to pregnant women	Nursing visits to puerperal women	Nursing visits to newborns	Nursing visits to infants
1995	50430	21646	28784	90686	92714	92373
1996	54056	25267	28789	113036	117991	101421
1997	55754	27756	27998	127003	136024	112316
1998	47068	30098	16970	134228	147593	111605
1999.	45179	28584	16595	132925	145714	106893
2000	43746	32032	11714	136976	149664	109607
2001	41209	30602	10607	138723	149975	113096
2002	40283	33206	7077	128857	143768	100567
2003	39848	29086	10762	139808	167536	101323
2004	40486	28225	12621	134672	155787	94660
2005	42678	25237	17441	135265	155540	81838
2006	41628	24397	17231	131300	154206	77834
2007	42070	26076	15994	149349	172951	86370
2008	43929	24243	19686	148468	172629	80571
2009	44754	24132	20622	148658	174201	78728
2010	43546	24966	18395	153170	179627	83836
2011	41342	24588	16754	156211	186571	82844
2012	41901	25384	16517	175357	207468	86095
2013	40083	23340	16743	154093	177242	75876
2014	39716	21105	18611	161016	180632	74427
2015	37666	18779	18887	152696	179163	67323
2016	37706	16874	20832	156631	167134	68049
2017	36705	13344	23361	166522	170936	71199
2018	37109	14070	23039	185475	156737	66986
Overall	**1,029,067**	**593,037**	**436,030**	**3,317,770**	**3,841,803**	**2,125,837**

Table 2 shows the number of nursing visits to pregnant women and childbirth in total and difference in the number of visits over a period of 24 years. There was a significant drop in the number of births but also in the number of visits to pregnant women. While nursing visits to puerperal women and newborns was rising, nursing visits to infants showed oscillations with a falling tendency.

According to the current health care standard in Croatia, pregnant women require community nurse visits once in pregnancy (after week 16), twice while the babies are newborns (with a simultaneous visit to the puerperal woman), and twice during the baby infancy.

Figure 1 shows a slight drop in visits to pregnant women, but also a clear falling tendency in community nurse visits to children. Furthermore, there was significant decline in the number of childbirths. The difference in the number of visits to pregnant women and number of childbirths has remained almost the same in Croatia since 1995 to this day, which only means that the health service did not use the opportunity to increase the number of nursing visits to pregnant women, which opened due to the fall in the number of pregnancies.

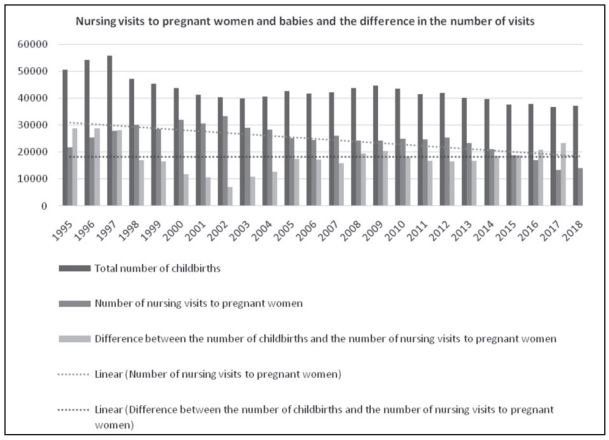

Figure 1. *Diagram illustrating the number of nursing visits to pregnant women and childbirth in total, difference between the two, and trend in the Republic of Croatia between 1995 and 2018.*

The community health (visiting nurse) service is provided by senior staff nurses specializing in community health care, at a standard of 5100 inhabitants *per* community nurse prescribed by the Ordinance on the standards and norms of healthcare rights pertaining to the basic health insurance plan (11). The number refers to the number of inhabitants covered by the competent outpatient clinic/organizational unit of the county outpatient clinic (11-13). In 2005, there were overall 871 community nurses and 4877 insurance beneficiaries *per* visiting nurse. In 2014, there were 897 community nurses (with secondary education and higher). According to data on health insurance beneficiaries, each nurse had on average 5063 beneficiaries in their care. In 2018, the situation deteriorated, so that there were 865 community nurses (secondary education and higher) but 5200 beneficiaries *per* nurse (15).

Looking at the number of visits to pregnant and puerperal women, it is quite clear that visits to puerperal women were on the rise, while visits to pregnant women were dropping (Figure 2).

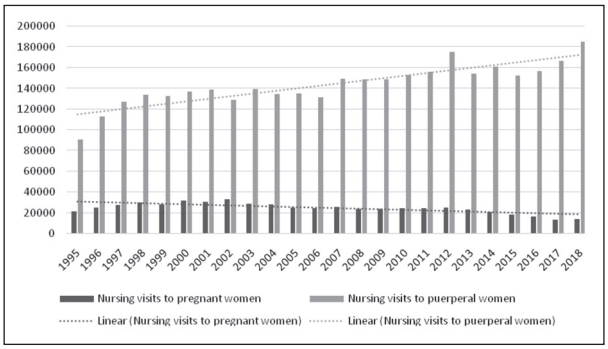

Figure 2. *Relationship between the number of nursing visits to pregnant and puerperal women and the observed trend, Republic of Croatia, 1995-2018.*

Judging by the data published, during the last observed year there were five nursing visits to puerperal women (5 visits; 185,475/37,109) while newborns (156,737/36,945) were visited somewhat less often (4.2 visits on average), which is twice the prescribed norm (10).

DISCUSSION

Securely attached children are adaptable, more independent, more respectful, more resilient to stress, and less impulsive. While growing up, they easily make friends and maintain friendships, develop social skills and achieve better academic success. As adults, they achieve closeness easily, form stable emotional relationships and establish better attachment with their children. Insecurely attached children are raised without a feeling of fundamental security and have extremely high stress hormone levels, which is a risk factor for healthy intellectual, emotional and social development. The consequences of neglecting emotional needs in children can lead to behavior disorders, depression, apathy, learning difficulties, and likelihood of developing chronic diseases. When compared with the securely attached, insecurely attached children are at a far greater risk of developing aggressive, destructive or asocial behavior. Disorders in attachment during the crucial first three years can lead to development of the 'non-empathetic personality disorder', where

the individual is incapable of entering into emotional relationships, is chronically angry or frustrated, has poor impulse control and an underdeveloped sense of morality and conscience (17).

A critical period for a family is the transition to parenting. The arrival of the first child brings about upsetting changes in the family development process (18). The changes that occur in parents' lives during the postpartum period are more negative than positive and equally disruptive for men as for women, and for their marriage (18). During the transition, three factors can impact parenting satisfaction, i.e. expectations before the baby is born, changes in communication, and pre-baby marital strain (18). With the birth of the baby, the center of family attention shifts (19). Optimal child development requires parental sensitivity and a harmonious atmosphere at home.

Mothers need social support, while fathers need understanding and support, and these needs remain largely unsatisfied. Mothers find the transition to parenting far more challenging, but traditionally receive far more support (20). Fathers' needs for support should not be neglected in order to ensure normal functioning, warmth and security within the family. By widening contacts to grandparents, the child sees a wider range of behaviors that can have an impact on his/her personality development (21). They can be sources of financial, instrumental and emotional support to the parents. The birth of a baby determines new intergenerational rules and relationships in the wider family. Relationships between parents and their primary families can change with the birth of a child, and vary from total dependence to independence (21,22). The past ten years have seen an increasing number of studies researching the links between wider family support through the affirmation of love and highlighting family relations through several generations. Multi-generational ties are becoming more important for well-being, as a form of support throughout a family life cycle (23).

Community health care is provided by senior staff nurses specializing in community care at a standard of 5100 inhabitants *per* visiting nurse, pursuant to the Ordinance on the standards and norms of healthcare rights pertaining to the basic health insurance plan (11). That number refers to the number of inhabitants covered by the competent outpatient clinic/organizational unit of the county outpatient clinic (11,13,14).

For pregnant women, the visit of a community nurse is important because of the early assessment of their health, and provision of support and information on all available health and social services related to improving their health, emotional and economic status (10,24).

Care for the mother and the child, including visits to gynecologists, starts when they leave the maternity ward. The first visit of the community nurse is thus the first visit to the newborn. In Croatia, when new mothers are discharged from the maternity ward, the usual procedure is for the hospital staff to inform the chief nurse of the competent outpatient clinic of the new mothers released the day before. The chief nurse then informs the community health nurse covering the place of residence of the new mother (12).

The legal and organizational framework of the health care system in the Republic of Croatia foresees community health service visits to pregnant women (10,11). The aim of such visits is to implement primary and secondary preventive measures by estimating medical, psychological, social and economic condition of pregnant women, their abilities to adopt new knowledge, skills, habits and attitudes concerning pregnancy and motherhood, and to detect vulnerability factors in a timely manner. Once pregnancy is determined, during the first gynecologic check up in pregnancy, the gynecologist's nurse informs the community health nurse of the new pregnant woman. The first visit takes place between the 4th and 5th month of pregnancy (10-12). This leaves ample room for interventions and preparation of mothers-to-be, their family and all those involved for the arrival of a new member of their community. Data on the Republic of Croatia and its counties show that there is major discrepancy in the number of reported nursing visits to pregnant women; more than half of all pregnancies end up without a single nursing visit. The data indicate that there are many unused opportunities and only few interventions in the families of pregnant women prior to the baby's birth, and that trend is visible throughout the observed period (12,13,15).

Care for the mother and the child starts with the visit of the community nurse to the pregnant woman and continues after birth with visits to puerperal women and newborns. Once the pregnant woman has visited her gynecologic clinic and they have determined her pregnancy, the gynecologic nurse informs the community health service of the new pregnant woman, providing basic data such as the pregnant woman's address and phone number so that the service can plan a visit. The first visit takes place between the 4th and 5th month of pregnancy. In Croatia, the usual procedure when the baby is born and the new mothers are discharged from the maternity ward is for the hospital staff to inform the chief nurse of the competent outpatient clinic of the mothers released the day before. The chief nurse then goes on to inform the visiting nurse in charge of the woman's place of residence that the new mother declared when registering at the hospital.

Pregnancy and the postpartum period are a good time to achieve a positive and permanent impact on the health and development of children. Intervention programs provide support and services that can fulfill the potentials of the community and meet the needs of the family. This is a unique opportunity to support children with the aim of fostering their potential for healthy development (25).

CONCLUSION

The results of this research indicate that there is an opportunity to intervene in the formation of the social dimensions of personalities in the earliest stages of life. The existing health care instruments, such as nursing visits to future mothers in their primary family setting, can be used to help the families adapt to the arrival of the new member and to encourage the fathers' and other family members' involvement to support the mother and her baby. The aim of such visits is to implement primary and secondary preventive measures by estimating medical, psychological, social and economic condition of pregnant women, their abilities to adopt new knowledge, skills, habits and attitudes concerning pregnancy and motherhood, and to detect vulnerability factors in a timely manner. This approach leaves ample room for interventions and for the preparation of future mothers, the family and all those involved, for the arrival of a new member of their community. Data indicate that the opportunities are being missed and that interventions in the family prior to the baby's birth are insufficient.

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SAŽETAK

TRUDNOĆA – NEISKORIŠTENE PRILIKE ZA PREVENCIJU I INTERVENCIJU U PATRONAŽNOJ SLUŽBI

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Privrženošću opisujemo duboku i trajnu emocionalnu vezu s drugom osobom. Privrženošću se primarno opisuje emocionalna veza između dojenčeta i majke, iako je privrženost svojstvena cjeloživotnom ljudskom ponašanju. Obilježava ju tendencija traženja i održavanja bliskosti privrženim ljudima za vrijeme stresnih situacija. Osjećaj sigurnosti nastao iz odnosa majke i djeteta stvara osnovno povjerenje ili nepovjerenje u odnosima te određuje vjerovanje djeteta o tome kako će okolina reagirati na njegove potrebe. U razvoju privrženosti važnu ulogu ima osjetljivost majke za potrebe djeteta, usklađenost majke i djeteta, temperament djeteta, majčina sjećanja iz njezina djetinjstva kao i podržavajuća okolina. Zdravo obiteljsko funkcioniranje vrlo je važno svim članovima obitelji, osobito trudnicama. Zdravstveni sustav trudnicama pruža potporu kroz sustav preventivnih posjeta patronažne službe. Od svih zdravstvenih djelatnika patronažna sestra je jedina koja ulaskom u dom i obiteljsku sredinu trudnice ima cjelokupan uvid u moguću pojavu rizičnih čimbenika za razvoj poremećaja povezanosti majke i djeteta. Ovom intervencijom možemo preventivno djelovati u cilju očuvanja fizičkog, psihičkog i socijalnog blagostanja. Cilj je bio utvrditi razlike u broju predviđenih i ostvarenih preventivnih posjeta patronažne sestre trudnicama u Hrvatskoj. Analiza je napravljena po županijama Republike Hrvatske i na razini cijele Hrvatske. Korišteni su podatci o zdravstvenoj zaštiti trudnica, babinjača i djece do godinu dana života objavljeni u hrvatskim zdravstveno-statističkim ljetopisima i izvješću o prirodnom kretanju stanovništva Državnog zavoda za statistiku u razdoblju od 1995. do 2018. godine. Prikazan je broj posjeta patronažne sestre trudnicama i djeci do godine dana života te razlika broja posjeta u Republici Hrvatskoj u razdoblju od 23 godine. Očevidan je značajan pad broja živorođenih, ali isto tako i pad broja posjeta trudnicama, a tendencija pada se nastavlja. U promatranom razdoblju prosječan broj trudnica (nakon 16. tjedna trudnoće) bez ijednog patronažnog posjeta je 42,5 %, a posljednjih godina taj postotak raste. Tako se propušta prilika da se toj osjetljivoj skupini pruži makar taj segment socijalne i stručne potpore i pomoći. Nije iskorišten prostor nastao smanjenjem broja trudnica za povećanje obuhvata posjetom patronažne sestre makar jednom u trudnoći. Broj posjeta babinjačama i novorođenčadi raste, dok broj posjeta trudnicama pada, pa je 2018. godine bez ijednog patronažnog posjeta bilo 62,1 % trudnica u Hrvatskoj. Zaključuje se kako nije iskorišten prostor nastao smanjenjem broja trudnica za povećanje obuhvata posjetom patronažne sestre makar jednom u trudnoći, a nakon 16. tjedna trudnoće. Patronažna zaštita trudnica nije dostigla predviđeni standard zdravstvene zaštite.

Ključne riječi: patronažna djelatnost, trudnice, organizacija zdravstvene zaštite, Hrvatska

GIRL WITH TAKAYASU ARTERITIS -PROGRESSIVE COURSE OF THE DISEASE AND MULTIPLE SURGICAL INTERVENTIONS

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Takayasu arteritis is a rare large-vessel vasculitis but it can be associated with high mortality rates in childhood. Granulomatous vasculitis usually affects the aorta and/or main branches but also coronary and pulmonary arteries. The course of the disease is unpredictable and management is based on controlling inflammation and preventing end-organ damage. In this case we describe a patient with progression of vasculitis but so far successful prevention of possible ischemic consequences using immunosupressive and biologic therapy and multiple surgical interventions over the course of the disease. A 14-year-old girl presented with precordial pain and numbness of the left arm. Physical examination revealed the absence of the radial pulse in the left arm. Computed tomography angiography showed subtotal occlusion of the left main coronary artery, subtotal occlusionof the left common carotid artery, subtotal occlusion of the left subclavian artery and stenosis of thoracic aorta below isthmus of aortae. Despite aggresive conservative therapy and cardiosurgical treatment the course of the disease was complicated with restenoses which were resolved with subsequent revascularization procedures. Here we present an adolescent girl with progressive vasculitis and with multiple surgical interventions. Carefully monitoring of the patient and good collaboration between pediatric cardiologist and rheumatologist with radiologists and cardiac surgeons improved life-quality of the patient which now studies at the University and has good physical and mental status.

Key words: **childhood Takayasu arteritis, progressive course, surgical interventions, revascularization**

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Abbreviations: c-TA: childhood Takayasu arteritis; CT: computed tomography; EULAR: European League Against Rheumatism; PRINTO: Pediatric Rheumatology International Trials Organization; PReS: Pediatric Rheumatology European Society

INTRODUCTION

Childhood Takayasu arteritis (c-TA) is rare but the commonest large vessel vasculitis in children, its incidence has been estimated to be 2,6/1,000,000 per year and it occurs more frequently in girls (1). Etiology is not completely understood but general theories include genetic factors, infections and activation of both humoral and cell-mediated immunity which lead to inflammation, tissue damage, scarring and stenoses of large vessels (2). Diagnosis is made upon European League Against Rheumatism (EULAR)/Pediatric Rheumatology International Trials Organization (PRINTO)/Pediatric Rheumatology European Society

(PReS) criteria which include pathology in angiography (magnetic resonance angiography is preferable in children to minimize exposure to radiation) plus one of the following: absence of peripheral pulses/claudication, asymmetrical blood pressure between arms, murmur over great arteries, hypertension or signs of systemic inflammation (elevated markers of inflammation) (3). Therapy options include early initiation of glucocorticoids, symptomatic therapy with beta-adrenergic blockers, calcium channel blockers and ACE inhibitors, use of immunosuppressive agents and surgical interventions (4). The course of the disease in our patient was progressive and complicated by new stenoses and restenoses after initial surgical treatment which required revascularization interventions.

PATIENT PRESENTATION

A 14-year-old girl presented to our Clinic with angina and numbness of the left arm. Physical exam revealed no palpable pulses in the left arm and arterial hypertension. Laboratory examination demonstrated elevated markers of inflammation (ESR 75 mm/h, CRP 50,9 mg/L). After initial examination and laboratory evaluation the diagnosis of c-TA was suspected. The patient was subjected to computed tomography (CT) angiography which showed subtotal occlusion of the left main coronary artery, subtotal occlusion of the left common carotid artery, subtotal occlusion of the left subclavian artery and stenosis of the thoracic aorta below isthmus of aortae. According to EULAR/PRESS/PRINTO classification (3), our patient fulfilled the following criteria: angiographic pathology plus four out of five additional criteria (absence of peripheral pulses, asymmetrical blood pressure between arms, hypertension and elevated markers of inflammation) so diagnosis of c-TAtype IIb (ascending aorta, aortic arch and its branches, thoracic descending aorta) (5),was made. The patient was treated following EULAR recommendations for the management of large-vessel vasculitis (4). We started high-dose glucocorticoid therapy maintained with prednisone and followed by adjunctive therapy with methotrexate and cyclophosphamide. Due to headaches, arterial hypertension, precordial pain and limb ischemia, after three months of initial conservative medical management, complex surgical treatment was performed: subtotal occlusion (90%) of the left main coronay artery was resolved by bypassing occlusion with right mammaria artery into the left anterior descending artery and obtuse marginal branch of the circumflex artery (Figure 1), an ascending aorta to the left carotid artery and left carotid artery to the left axillary artery conduits were placed to resolve stenoses of the left common carotid artery and subtotal occlusion of the left subclavian artery (Figure 2). Finally, a stent was inserted into the stenotic descending thoracic aorta (Figure 3c).Two months after surgical repair severe flare of the disease occured so biologic therapy (rituximab) was introduced. Despite agressive conservative and surgical management over the next two years, the girl developed stenosis of the proximal segment of previously inserted conduit between an ascending aorta to the left common carotid artery (Figure 3a) and additional stenosis of the right common carotid artery. An anastomosis between left and right carotid artery was created (Figures 2, 3b) and stent was placed into the stenotic segment between ascending aorta and the left carotid artery (Figure 3c). In the following course, due to further stenosis of the right common carotid artery, an anastomosis between right subclavian artery and distal segment of the right common carotid artery, just above the stenosis, was made (Figure 2). After complex and multiple surgical interventions the patient is in good condition, she studies at the University and her NYHA score is I-II. At the latest follow-up she was complaining about postprandial abdominal pain so she was admitted to hospital. Clinical presentation of abdominal angina required exclusion of mesenteric ischemia. CT angiography showed completely normal abdominal aorta and branches. Currently we are investigating the other possible causes of the abdominal pain having in mind rare but possible coexistence of c-TA and inflammatory bowel disease. Also due to the signs and symptoms of left hand ischemia, we performed CT angiography which showed a subocclusive lesion of the left axillary artery, about 40 mm long. Therefore, with left transradial approach, we performed a successful endovascular revascularization of the left axillary artery by using a 4×40 mm balloon predilatation (Armada 18, Abbott Vascular, USA) and implanted a heparin stent graft with dimension 5×50 mm (Viabahn, Gore, USA) (Figure 4).

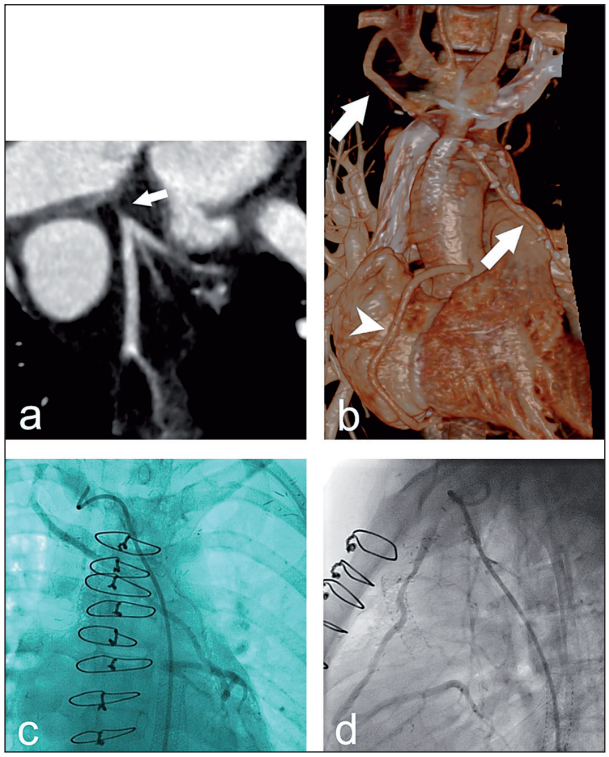

Figure 1. a) Coronary CT angiography, multiplanar reformation. Subocclusive stenosis (lesion) of left main (LM) coronary artery (arrow). b) Coronary artery bypass graft (arrows): right internal mamarian artery (RIMA) revascularizing left anterior descending (LAD) and obtuse marginal (OM) arteries. Normal right coronary artery (arrowhead). c) Coronary angiography of the LM coronary artery bypass with RIMA to the circumflex artery. Normal coronary perfusion after intervention. d) Coronary angiography, lateral view.

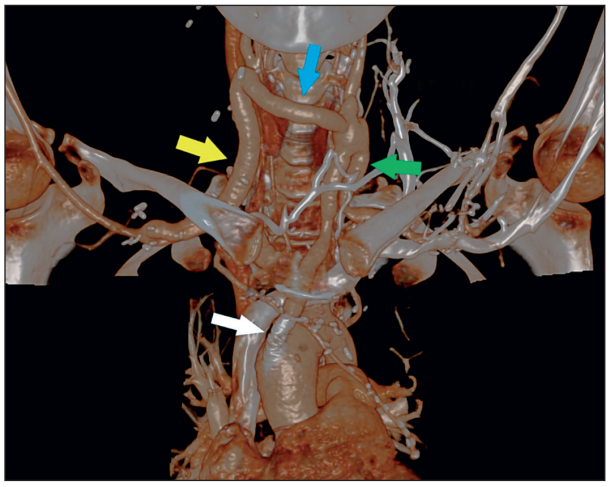

Figure 2. CT angiography – bilateral subocclusion/stenosis of common carotid artery (ACC), and left subclavian artery. Bypass from ascending aorta to the left ACC and stent placement into the stenotic part (white arrow). Bypass from the left ACC to the left axillary artery (green arrow), bypass between right and left ACC (blue arrow), bypass from the right subclavian artery to the right ACC (yellow arrow).

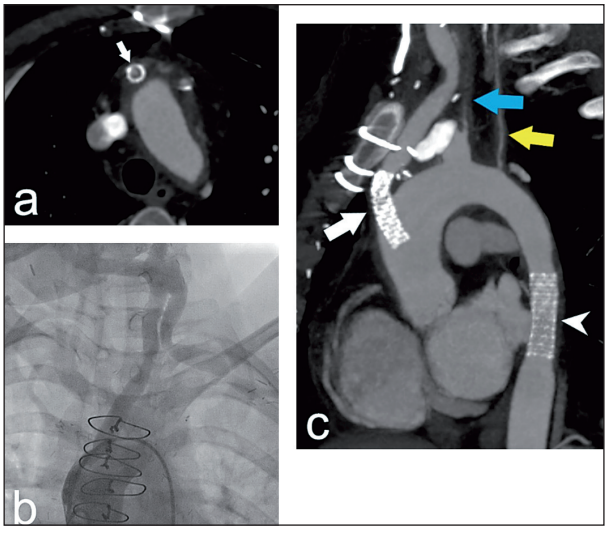

Figure 3. a) CT angiography- restenosis in the stent placed at the stenotic part of the bypass between ascending aorta and left ACC (white arrow). b) Catheter angiography - stenosis of the bypass between ascending aorta and left ACC. Bypass between left ACC and left axillar artery due to stenosis of the left subclavian artery. Bypass between left and right ACC due to severe stenosis of the right proximal part of ACC. c) CT angiography – stent placed into aortocarotid (left) bypass (white arrow), stent placed in stenotic part of descending aorta (arrowhead). Subocclusive stenoses of the left ACC (blue arrow) and left subclavian atery (yellow arrow).

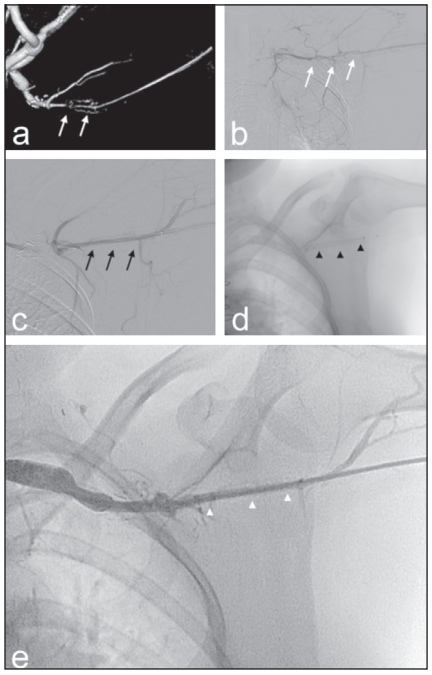

Figure 4. a) b) CT angiography (VRT reformatted image) and DSA angiography, subocclusive lesion of left axillary artery and numerous collateral arteries (white arrows) c) Significantly better width and normal patency of the artery after balloon predilatation (black arrows) d) Stent graft endoprosthesis with heparin bioactive surface implanted in axillary artery (black arrowheads) e) Normal width and patency of the axillary artery after stent graft implantation, with significantly lesser collateral arteries (white arrowheads).

DISCUSSION

Takayasu arteritis can be very challenging due to unpredictable and progressive course of the disease and possible endorgan damage. There have been no randomized therapeutic trials in pediatric patients and most evidence has been derived from studies performed in adults (2). In 2009. EULAR established recommendations for the management of large vessel vasculitis in adults (4). Russo and Katsicas have listed efficacy studies in Takayasu arteritis including pediatric patients (2). Recently published European consensus-based recommendations for diagnosis and treatment of rare pediatric vasculitides - the SHARE initiative, concluded, considering the lack of evidence in children, that EULAR recommendations may be used in paediatric Takayasu arteritis patients. It also acknowledged reports of the use of TNF-blockade, anti-IL-6 therapy and/or rituximab for severe disease (6). According to EULAR recommendations and SHARE initiative, reconstructive surgery for Takayasu arteritis should be performed in the quiescent phase of disease in the expert centres. Surgery during acute phase of the disease carries significant risk of re-occlusion and procedural complication (4,6). Arterial reconstruction and bypass grafting may be necessary in up to 70% of patients with Takayasu arteritis (4). In children, at least one third will require surgical interventions (2). The indications for surgical intervention include: hypertension from stenotic coarctation of the aorta or renovascular disease, end-organ ischemia or peripheral limb ischemia, cerebral ischemia, aortic or other arterial/cardiac aneurysms, or aortic regurgitation (6,7). Revascularization procedures may be open surgical (bypass interventions) or endovascular (stenting or balloon angioplasty). Both procedures carry substantial risk for the most common complication - restenosis of the vessel undergoing intervention (8). There are few studies in perioperative, short- and long-term outcome of the vascular procedures in children with c-TA but they concluded that children could benefit from this procedures with low mortality, morbidity, and satisfactory long-term results (9,10). Our patient had supra-aortic, subclavian, thoracic and coronary involvement. In adults, surgical approaches vary between different expert centers. For supra-aortic disease, open surgery is recommended with aorto-carotid bypass being the most commonly used techniqe. Upper limb claudication is one the most frequent indications for revascularization procedures but some centers recommend to avoid interventions if possible and advise upper limb exercise to promote development of collateral circulation. Treatment of thoraco-abdominal lesions include open surgery using prosthetic grafts or endovascular approaches using stent grafts (11). For coronary artery involvement literature suggests coronary artery bypass grafting which is associated with better long term results (8,11). Our patient reported symptomatic improvement after surgical management. During follow-up period we carefully monitor her clinical and laboratory status and depending on her symptoms and signs we performed follow-up imaging. Good collaboration between pediatric cardiologists/rheumatologists and radiologists, ophtalmologists, nephrologists, neurologists and vascular/cardiac surgeons guaranteed good assessment of the disease. The course of c-TA is progressive with repeated flares and need for continuous immunosupressive therapy (2). Recently published the largest study describing the clinical course and prognostic factors associated with rehospitalization of 101 Chinese pediatric patients with c-TA, found that type IIb in their cohort, represents 3.1-fold risk predictor of c-TA relapse and indicates a trend for vascular complications. They also showed revascularization to be an independent protective factor of fewer events and flares in c-TA. Finally they concluded that the stroke, elevated CRP, lower BMI level, and younger age at admission are independent risk factors of poor outcomes (12). Despite flares and multiple surgical interventions, our patient is in good condition (NYHA I-II), her blood pressure is well controlled (<90.c.), her latest markers of inflammation are normal and she succedes to manage all school responsibilities.

CONCLUSION

Due to rarity of the disease and lack of evidence in treating children with Takayasu arteritis it can be very challenging to manage this condition in pediatric population. Early diagnosis, regular clinical, laboratory and imaging follow-up, adequate therapy (conservative and surgical) and finally, cooperation between specialists can provide good quality of life to the patients.

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S A Ž E T A K

DJEVOJKA S TAKAYASU ARTERITISOM PROGRESIVNOG TIJEKA S MULTIPLIM KIRURŠKIM INTERVENCIJAMA

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Takayasu arteritis je vaskulitis velikih krvnih žila koji zahvaća aortu i njezine ogranke ali i pulmonalne i koronarne krvne žile. Tijek bolesti je nepredvidiv i terapija obuhvaća smirivanje upalnog procesa i prevenciju oštećenja organa. Prikazujemo bolesnicu s progresivnim tijekom bolesti koji je zasada uspješno obuzdavan uz pomoć imunosupresivne i biološke terapije kao i multiplim kirurškim postupcima. 14-godišnja djevojčica se očitovala prekordijalnim bolovima i utrnućem lijeve ruke s gubitkom pulsa radijalne arterije. CT angiografijom je nađena totalna okluzija debla lijeve koronarne arterije, subtotalna okluzija lijeve zajedničke karotidne arterije i lijeve potključne arterije te stenoza torakalne descendentne aorte ispod razine istmusa. Unatoč agresivnoj konzervativnoj terapiji i kardiokirurškom tretmanu daljnji tijek bolesti je kompliciran restenozama koje su razriješene postupcima revaskularizacije. Pažljivim praćenjem bolesnice kao i dobrom suradnjom pedijatrijskih kardiologa i reumatologa s kardiokirurzima te radiolozima omogućena je dobra kvaliteta života u djevojke koja se uspješno školuje te je u dobrom fizičkom i mentalnom stanju.

Ključne riječi: **pedijatrijski Takayasu arteritis, progresivan tijek, kirurške intervencije, revaskularizacija**

AORTO-LIJEVO VENTRIKULSKI TUNEL – DIJAGNOZA U FETALNOJ I LIJEČENJE U RANOJ NEONATALNOJ DOBI KAO PREDUVJET USPJEŠNOG ISHODA BOLESTI

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Prikazujemo pacijenta s aorto-lijevo ventrikulskim tunelom (ALVT, engl. *aorto-left ventricular tunnel)* kojemu je dijagnoza postavljena u gestacijskoj dobi (GD) od 27 tjedana. Indikaciju za pregled postavio je opstetričar zbog kardiomegalije. Ona se očitovala izrazitom dilatacijom lijeve klijetke (LVIDd 32 mm, >2SD), značajno smanjenom sposobnosti kontraktilnosti (EF 40 %) i obojenim doplerskim prikazom asimetrične insuficijencije aortalne valvule putem kanala koji ide od sinotubularne konekcije do lijeve klijetke, između interventrikulskog septuma i subinfundibularnog trakta desne klijetke. Ventrikulska učinkovitost (engl. *Myocardial Performance Index* –MPI ili Tei indeks) bio je 0,62 (n.v. 0,25-0,50), kardiovaskularni profil (engl. *Cardiovascular Profile Score* – CVPS) prema Huhtai 4 (normalno 10), a-val u duktus venozus (DV) pozitivan (++) (kao siguran dokaz srčane insuficijencije kod fetusa) i pozitivne pulsacije u umbilikalnim venama. Uz to je nađena ekstremna dilatacija tubularne aorte (18 mm – >2 SD, iznad 95. percentile). Prsten aortalne valvule u toj gestacijskoj dobi iznosi 5,8 mm (75. percentila), a širina ekstravalvularnog tunela 4-5 mm. Intrauterino se ne provodi medikamentno liječenje jer nije nađen hidrops. I postpartalno se nalazi kardiomegalija (rendgenska slika), a ehokardiografski potvrđuje dijagnoza ALVT-a. Kanal se nalazi iznad desnog koronarnog kuspisa, odnosno ispred rafe koja spaja lijevi i desni koronarni kuspis tako da se nalazi i dijagnoza bikuspidalne aortalne valvule (BAV) anteroposteriorne orijentacije. Zbog razvoja srčane insuficijencije ordinira se inotropna i diuretska terapija. Dijagnoza je potvrđena i MSCT-om te kateterizacijom srca (angiokardiografija). Kardiokirurška operacija učinjena je u dobi od 16 dana postavljanjem autologne perikardijske zakrpe (engl. *patch*) na aortalni otvor kanala. Postpartalno se ordinira diuretik, digitalis i ACE inhibitor. Postupno dolazi do oporavka lijeve klijetke (3 mjeseca nakon operacije EF 50 %), ali perzistira patološka dilatacija tubularne aorte. Očekuje se potpuni oporavak lijeve klijetke uz potrebu daljnje opservacije bolesnika zbog bikuspidalne aortalne vavule s mogućim reperkusijama na samoj valvuli i uzlaznoj aorti. U dobi od 10 mjeseci nađena je uredna kontraktilnost lijeve klijetke (EF 65 %), blaga aortalna insuficijencija (centralna), uz uredan protok kroz aortalnu valvulu, ali dalje postoji dilatacija uzlazne aorte (promjer 2,1 cm, >2 SD).

Ključne riječi: **aorto-lijevo ventrikulski tunel, prenatalna dijagnoza, srčana insuficijencija, rana kardiokirurška terapija, fetalna kardiologija, rijetke bolesti**

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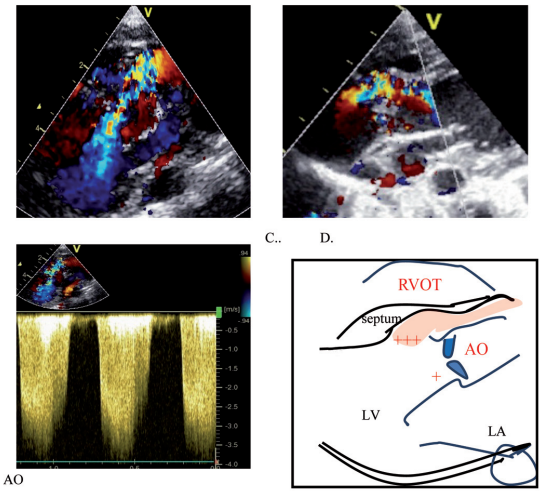
UVOD

Aorto-lijevo ventrikulski tunel (ALVT, engl. *Aorti-co-left ventricular tunnel)* je iznimno rijetka prirođena srčana grješka (PSG) koja je prvi put točno definirana i opisana 1963. godine (Levy i sur.) i objavljena kao „*Special Article*" u uglednom časopisu *Circulation* (1). Ipak i prije se anomalija opisala u okviru diferencijalno-dijagnostičkih dvojbi oko abnormalnih kanala koji se prikazuju između aorte i klijetki (rupture sinusa Valsalve, koronarne fistule, VSD s prolapsom koronarnog kuspisa), a koji su uglavnom posljedica hemodinamskih opterećenja te upalnih i degenerativnih promjena tijekom života (2). Značenje prvog Levyjevog opisa jest u dokazu da je ALVT prirođena srčana grješka, dakle grješka nastala tijekom embrionalnog razvoja srca, a

očituje se formiranjem patološkog kanala s početkom na sinotubularnom spoju i završetkom najčešće u lijevoj (90 %), a rijetko u desnoj (10 %) klijetki. Tijek tunela je paravalvularni, na način da dodiruje aortalni prsten na različitim razinama u njegovoj cirkumferenciji. Teče kroz ekstrakardijalno tkivo koje razdvaja subpulmonalni infundibulum od aorte i završava u lijevoj klijetki. Kasnije su rijetki autori opisivali pojedinačne nalaze ALVT-a u ranoj ili kasnijoj dječjoj dobi (3,4), a neki i u adultnoj dobi (5). Prva klasifikacija i mogući kardiokirurški pristup opisani su 1988. godine (6). S razvojem ehokardiografije i drugih metoda, oko 2000-te godine ALVT poprima svoje današnje značenje (7,8) u dijagnostičkom i terapijskom pristupu, ali se i dalje opisuje u časopisima s rijetkim bolestima (9). Naglim povećanjem senzitivnosti nalaza u fetalnoj kardiologiji koncem prošlog stoljeća ostvaruju se mogućnosti i prenatalne dijagnoze ALVT-a fetalnom ehokardiografijom (10,11). Iako dosada u svijetu nije opisano više od 200 djece s ALVT-om (12), a godišnje se u Europi dijagnosticira ALVT tek u oko 20-tak fetusa, od fetalnog se kardiologa očekuje dijagnoza ove rijetke prirođene srčane grješke. Cilj rada je prikazati dijagnozu ALVT-a fetalnom ehokardiografijom i njegovo liječenje rano postnatalno, a sporedni cilj je dati opsežniji osvrt na ovu rijetku grješku u raspravi s pregledom relevantne literature.

PRIKAZ BOLESNIKA

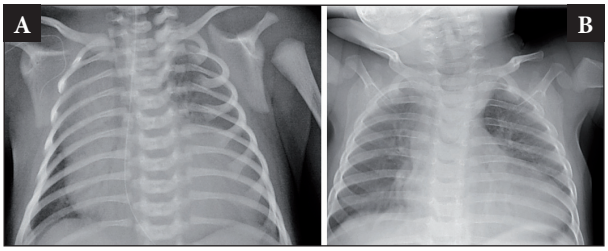
Riječ je o muškom djetetu rođenom iz treće, kontrolirane trudnoće. Iz prve trudnoće rođeno je zdravo dijete, a druga trudnoća je završila spontanim pobačajem u 12. tjednu. Naš je pacijent upućen na pregled fetalnom ehokardiografijom zbog sumnje na izrazitu kardiomegaliju u gestacijskoj dobi (GD) od 27 tjedana. Sumnja je potvrđena na osnovi patoloških parametara: kardiotorakalni indeks (CTI) 0,56 (n.v. 0,25-0,35), srčana os >60° (n. 43±7°), izrazita dilatacija lijeve klijetke (LVIDd 32 mm, >95. percentile) i značajno smanjena kontraktilnost LV (EF ≈ 40 %). Nalazi se i izrazita dilatacija uzlazne (tubularne) aorte od 18 mm (>95. percentile). Uočava se široki korijen aorte ukupnog promjera (16-18 mm), a obojenim se doplerom prikazuje izrazito asimetrična insuficijencija aortalne valvule, pa se posumnja na tunel između ascendentne aorte i lijeve klijetke koji je razlog kardiomegalije i srčane insuficijencije. Srčana je insuficijencija procijenjena s nekoliko parametara; ventrikularna učinkovitost (engl.*Myocardial Performance Index* –MPI ili Tei index) bio je 0,62 (n.v. 0,25 - 0,50), a-val u duktusu venozusu Arantii pozitivan (++) kao i prisutne pulsacije umbilikalne vene (siguran dokaz srčane insuficijencije kod fetusa), a kardiovaskularni profil (engl. *Cardiovascular Profile Score* – CVPS) prema Huhtai bio je 4 (normalno 10). Iako je ukupan promjer na razini aortalne valvule mjeren 16-18 mm, pozornim promatranjem ušća i odvajanjem paravalvularnog sistoličko-dijastoličkog protoka izmjeri se normalan promjer aortalnog prstena za tu gestacijsku dob (5,8 mm - 75. percentila), a širina ekstravalvularnog tunela 4-5 mm. Nalaz obojenim doplerom pokazuje jasno paravalvularnu insuficijenciju visokog stupnja (+++), dok na razini same valvule nalazimo tek trivijalnu insuficijenciju. Stenoze se ne nalazi (brzina u uzlaznoj aorti 0,9 m/sek) (sl. 1 A, B, C, D). Dilatacija lijeve klijetke smatra se posljedicom asimetrične insuficijencije aortalne valvule koja upućuje na postojanje aorto-lijevo ventrikulskog tunela. Dilatacija uzlazne aorte istovremeno ukazuje na postojanje bikuspidne aortalne valvule anteroposteriorne orijentacije, ali taj nalaz intrauterino nismo mogli sa sigurnošću potvrditi. Medikamentna terapija intrauterino nije provedena, jer nema hidropsa unatoč patološki sniženog CVPS-a. Kontrolni fetalni ehokardiografski nalaz nije pokazivao pogoršanje srčane insuficijencije u trećem trimestru.



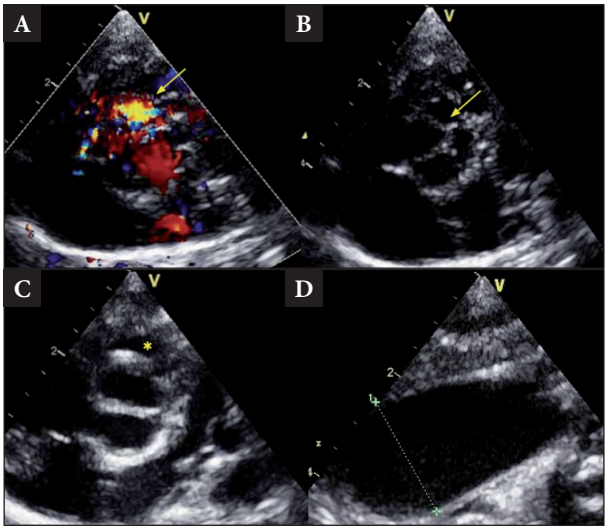
Sl. 1 ***A.*** *Ehokardiografski nalaz ALVT u GD od 27 tjedana - prikaz obojenim doplerom – asimetrična insuficijencija aortalnog ušća paravalvularno između koronarnih kuspisa i septuma. Visokog je stupnja i dopire do vrška srca.* ***B.*** *Prikaz asimetrične aortalne insuficijencije obojenim doplerom s izoliranim prikazom tunela između aorte i lijeve klijetke. Veliki dio insuficijencije odvija se u patološkom tunelu (+++), manji dio kroz valvulu (+).* ***C.*** *Doplerski prikaz insuficijencije* ***D.*** *Shematski prikaz ALVT-a (duga os); RVOT - izlazni trakt desne klijetke, LV lijevi ventrikul, AO aorta, LA lijevi atrij*

Trudnoća je dovršena u 39+1 tjednu gestacije, vaginalnim porođajem, stav glavicom, RM 3530 g, RD 51 cm, Apgar 9/10. Nakon porođaja dijete je bilo vitalno, urednih fenotipskih obilježja. Kliničkim pregledom nalazi se umjereno povećana jetra, prekordijalno čuo se grublji sistoličko-dijastolički šum nad bazom, srčana akcija bila je ritmična, frekvencije 140-150/min, periferne pulzacije su bile snažne (*pulsus celler et altus*), a arterijski tlak divergentan ⌠RR: desna ruka 86/40 (53) mm Hg, lijeva ruka 78/35 (51) mm Hg⌡. Dijete je u trećem satu života bilo premješteno u Zavod za neonatologiju i intenziv-

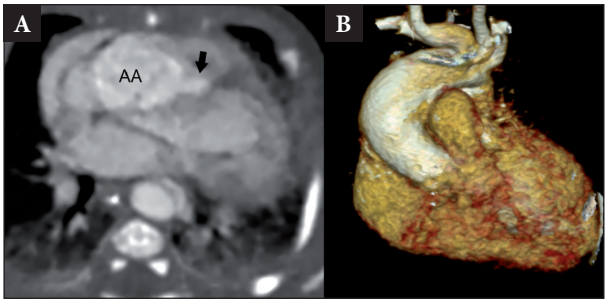
no liječenje. Od trećeg dana života uvodi se inotropna potpora dobutaminom uz diuretik zbog porasta srčane frekvencije (180/min) uz tahidispneju, što ukazuje na razvoj rane srčane insuficijencije, ponajprije uzrokovane insuficijencijom "aortalnog ušća". Rendgenska slika torakalnih organa novorođenčeta očituje se izrazitom kardiomegalijom na račun lijeve klijetke i sumnje na dilataciju uzlazne aorte. Diferencijalnu dijagnozu remeti veliki desni režanj timusa (sl. 2A). Elektrokardiografski nalazimo sinusni ritam sa semivertikalnom električnom osi, PQ 0,14", QRS 0,04", QTc 0,479 (n. do 0,460), hipertrofiju lijeve klijetke (RV5+SV2 60 mm), teže smetnje repolarizacije (T valovi negativni od V1-V6). Ehokardiografski se potvrđuje sumnja na ALVT, a na prvom se pregledu nalazi i Botallov duktus s gradijentom između aorte i plućne arterije 25-30 mm Hg što označava očekivano visok tlak u plućima postpartalno. Nalaz iz duge osi nije se razlikovao od fetalnog nalaza, ali iz kratke osi nalazimo dodatne informacije. Tunel se nalazi paravalvularno u blizini rafe između desnog i lijevog koronarnog kuspisa, više pozicioniran iznad desnog koronarnog kuspisa. Time se potvrđuje i nalaz bikuspidne aortalne valvule anteroposteriorne orijentacije. Aortni prsten je normalnog promjera (9-10 mm), širina tunela je 4-5 mm, a ukupni promjer na razini aortalnog prstena, koji uključuje i prikazani tunel, iznosi 16 mm. Dilatacija uzlazne aorte potvrđena je ehokardiografski, ukupnog promjera 18-20 mm (sl. 3 A,B,C, D). Peti dan boravka učinjen je MSCT pregled koji potvrđuje prethodno opisanu dijagnozu, a prikazuje i paravalvularni kanal (sl. 4A, označeno strjelicom). Na 3D slici potvrđuje se još jednom izrazita dilatacija uzlazne aorte i sumnja na dodatnu dilataciju ogranaka aortnog luka, osobito brahiocefaličnog trunkusa (sl. 4 A i B). Dan nakon toga učinjena je kateterizacija srca s angiokardiografijom. Na desnoj strani srca nema patoloških promjena. Na lijevoj strani nalazimo visok end-dijastolički tlak lijeve klijetke (16 mm Hg), bez gradijenta nad aortalnom valvulom i divergentni arterijski tlak u aorti ⌠84/32(49) mm Hg⌡. Angiografski se prikazuje ALVT promjera 6 mm, anteriorno, između koronarnih kuspisa i septuma s masivnom regurgitacijom kontrasta (+++) te trivijalnom insuficijencijom aortne valvule (+). Opisana je izrazito dilatirana uzlazna aorta (promjera 20 mm), širok luk aorte (promjera 14-16 mm) i značajno proširene sve tri grane aortalnog luka, osobito brahiocefalički trunkus (sl. 5 A,B**).** Duktus se više ne nalazi, već samo njegov divertikul. Iako je opće stanje pacijenta nakon poroda bilo zadovoljavajuće zamijetila se postupna dekompenzacija lijeve klijetke (ultrazvučnim pregledom srca opisana je povećana lijeva klijetka sa značajno oslabljenom kontraktilnosti - EF 35 %). Postavljena je hitna indikacija za korekciju koja je i učinjena 16-og dana života. Kardiokirurg opisuje paravalvularni tunel lateralno i kaudalno od desnog koronarnog ušća, promjera 5 mm. Tunel je zatvoren autolognom perikardijalnom zakrpom (engl. *patch*). Nije učinjena korekcija uzlazne aorte (zbog visokog rizika zbog očekivanih histoloških promjena u uzlaznoj aorti). Na operaciji i u postoperacijskoj njezi nije bilo komplikacija. Postoperacijski prima digitalis, diuretike (Furosemid, Aldakton) i ACEi. Postoperacijski ultrazvučni nalaz srca je ukazivao na insuficijenciju na razini same aortalne valvule stupnja I. Tri mjeseca nakon operacije kontraktilnost lijeve klijetke je značajno poboljšana (EF 50 %), a uzlazna aorta je i dalje patološki dilatirana, zajedno s aortalnim ograncima. U dobi od 10 mjeseci nalazimo sljedeći ehokardiografski nalaz: uredna kontraktilnost lijeve klijetke (EF 65 %), blaga aortalna insuficijencija (centralna), uredan protok kroz aortalnu valvulu, dilatacija uzlazne aorte, širina 2,1 cm (>2 SD). Dijete uredno napreduje. U dobi od 10 mjeseci TM 8,8 kg (10-25. c), TV 75 cm (75. c). U terapiji prima ACEi.



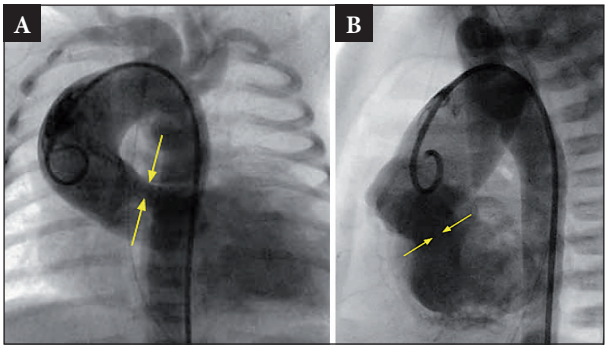
Sl. 2 ***A.*** *Rendgenska slika torakalnih organa novorođenčeta s aorto-lijevo-ventrikulskim tunelom očituje se izrazitom kardiomegalijom na račun lijeve klijetke i sumnje na dilataciju uzlazne aorte. Diferencijalnu-dijagnozu remeti veliki desni režanj timusa pri porođaju (A). Rendgenski prikaz u dobi od 10 mjeseci* ***(B)***



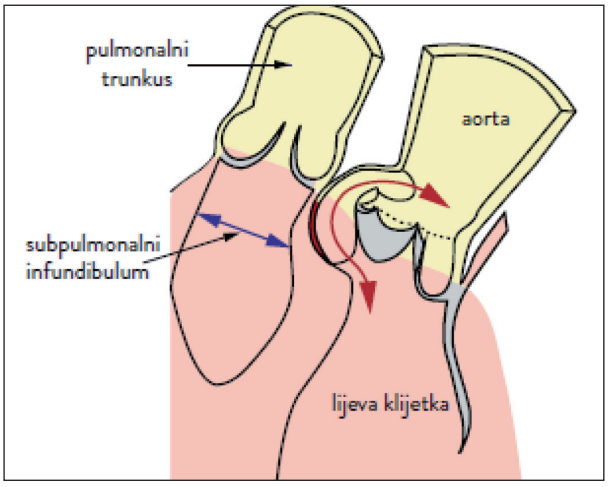
Sl. 3 ***A.*** *Postpartalni prikaz obojenim doplerom asimetrične insuficijencije iz kratke osi na razini aortalnog ušća; tunel se nalazi lateralno i kaudalno od desnog koronarnog kuspisa ili ispred rafe između desnog i lijevog koronarnog kuspisa (strjelica),* ***B.*** *Ortogradni presjek kroz aortalno ušće na kojem je vidljivim rafe (sraštenje-nerazdvajanje) lijevog i desnog koronarnog kuspisa (slika anteroposteriorne orijentacije bikuspidalnog aortalnog ušća). Ispred rafe, više na desnom koronanom kuspisu nalazi se tunel.* ***C.*** *Funkcionalno bikuspidalna aortalna valvula ispred koje se nalazi tunel (zvjezdica).* ***D.*** *Izolirani prikaz aneurizmatske dilatacije ascendentne aorte ehokardiografski.*



Sl. 4. ***A.*** *MSCT prikaz ALVT-a (strjelica), AA-uzlazna aorta,* ***B.*** *MSCT 3D prikaz*



Sl. 5. ***A.*** *Angiografski prikaz aorto-lijevo ventrikulskog tunela u novorođenčeta; u cijelosti povećano srce na račun dilatirane lijeve klijetke, ekstremno široka aorta koja ispunjava veći dio desnog gornjeg prsišta, promjera 2 cm, prikaz tunela (strjelice) koji čini oko jednu trećinu ukupnog promjera aortalnog ušća i uzrok je masivne insuficijencije kontrasta injiciranog u ascendentnu aortu. Uz tubularnu aortu proširen je i luk aorte te sve tri grane luka aorte. Vidi se i divertikul Botallova duktusa (posteroanteriorna projekcija).* ***B.*** *Lateralna projekcija; izrazito široka tubularna aorta koja ispunjava prednji medijastinum gotovo u cijelosti. Tunel se nalazi na razini koronarnih kuspisa (strjelica) kao uzrok masivne insuficijencije i uzrok je dilatacije lijeve klijetke.*



Sl. 6. *Paravalvularni tunel između aorte i lijeve klijetke (crvena strjelica) koji počinje na sinotubularnom spoju, teče putem ekstrakardijskog tkiva i otvara se u lijevoj klijetki.*

RASPRAVA

Patološka anatomija, moguća etiopatogeneza i epidemiologija

Aortoventrikulski tunel (AVT) je prirođena srčana grješka koja se očituje postojanjem paravalvularnog kanala između uzlazne aorte i lijeve (90 %), odnosno desne (10 %) klijetke (8). Zbog značajno učestalije komunikacije prema lijevoj klijetki u literaturi se najčešće prikazuje aorto-lijevo ventrikulski tunel (ALVT) (1,3-7,12). Ušće ovog kanala počinje na sinotubularnom spoju i premošćuje cirkumferenciju aortalne valvule na različitim mjestima, a najčešće (oko 4/5) u bliskom odnosu s desnim koronarnim kuspisom (3,8,13), premda se može naći i ispred rafe koja predstavlja nerazdvajanje lijevog i desnog koronarnog kuspisa (8). Kod našeg bolesnika tunel smo dijagnostičkim metodama prikazali upravo na tom mjestu, a najmjerodavnije kardiokirurško izvješće navodi tunel promjera 5 mm koji se nalazi paravalvularno lateralno i kaudalno od desnog koronarnog kuspisa. Početak tunela nalazi se uvijek kao prstenasti otvor na sinotubularnom spoju (spoj između sinusa aortalne valvule i ascendentne aorte), teče putem ekstrakardijskog tkiva i završava najčešće kao ovalni otvor u lijevoj klijetki subvalvularno, prije pojave muskulature interventrikulskog septuma. Histološki presjek ušća na sinotubularnom spoju sadrži fibrozno tkivo, glatke mišićne stanice i elastična vlakna i teče u ekstrakardijskom tkivu razdvajajući desnostrani subinfundubulum od aortnog prstena. To je važno za diferencijalnu dijagnozu prema koronarnim fistulama koje se otvaraju u kavitet lijeve klijetke putem miokardijskih rascjepa, a bez paravalvularnog premoštenja (8). Dosada u domaćoj literaturi nismo našli prikaz bolesnika s aortoventrikularnim tunelom ni u jednoj dobnoj skupini, pa ni u fetusu, pa smatramo da je ovo prvi takav prikaz. Ekstrakardijsko tkivo odvaja subpulmonalni infundibulum od aorte (sl. 6) (8). Rad Levyja i sur. iz 1963. godine smatra se prvim opisom ALVT-a zbog činjenice da je tim radom ovaj rijetki entitet dokazan kao prirođena srčana grješka (1), premda se mora dodati da su prethodno Burchel i Edwards 1957. godine razmatrali druge diferencijalno-dijagnostičke probleme koji se očituju komunikacijom između aorte i klijetki (desne ili lijeve), ali su većinom opisivani nalazi koji su posljedica hemodinamskih, upalnih ili degenerativnih promjena tijekom života ili pripadaju VSD-u s prolapsom koronarnog kuspisa u desnu klijetku (2). Opisani su defekti koji se javljaju izolirano (defekti iznad i ispod desnog aortalnog kuspisa, defekti ispod posteriornog aortalnog kuspisa, defekti iznad i ispod lijevog aortalnog kuspisa) ili kao kombinirani defekti između aortalnog korijena i srca. Većina diferencijalno-dijagnostičkih dvojbi može se riješiti tako da se kao osnova uzme izvor kanala na sinotubularnom spoju, dok drugi nalazi imaju svoj

početak ispod toga spoja. Teža je distinkcija prema koronarno-ventrikulskim fistulama, jer koronarno-arterijsko ušće može započeti iznad sinotubularnog spoja, a lijeva koronarna arterija, a. cirkumfleksa i desna koronarna arterija mogu komunicirati unutar samog aortoventrikulskog tunela (1,7,8,14-17). Ipak, učestalo pridružena fistula aorto-lijevo ventrikulskom tunelu dopušta pretpostavku o zajedničkom etiološkom čimbeniku u razvoju pa još više pridonosi tvrdnji da je ALVT prirođena srčana grješka. Ipak, neki slučajevi ALVT-a imaju pridruženu anomaliju aortalne valvule (rascjep prednjeg kuspisa na dvije hemikomisure), pa u kliničkoj slici dominira insuficijencija same aortalne valvule unutar i izvan njezine cirkumferencije (prstena). Zato se nekada dijagnozu može točno postaviti tek *intra operationem* (18). Kod našeg bolesnika nije bilo rascjepa aortalnog listića i sama je valvula u hemodinamskom smislu riječi bila kompetentna, ali je jasan nalaz bikuspidalne aortalne valvule anteroposterione orijentacije (tip I) ispred čije se poveznice nalazio ALVT (djelomična razlika u tumačenju nalaza prije operacije i *intra operationem*). Kod većine se bolesnika nalazi aneurizmatski proširenu uzlaznu aortu, a potvrđene su histološke promjene u stijenci aorte u bolesnika 15 godina nakon zatvaranja tunela. Nalaz je ukazivao na cistične promjene u stijenci aorte (11). Postoji velika povezanost s razvojnom teorijom aortalnih i plućnih zalistaka, odnosno jastučića iz kojih se razvijaju aortalni i plućni sinusi kao i njihove pripadajuće valvule koje se odvajaju ekstrakardijalnim tkivom (5,19). S obzirom da se u dijelu bolesnika s ALVT-om nalazi i bikuspidalna aortalna valvula (BAV) sa svim mogućim i progresivnim morfološkim i posljedičnim hemodinamskim posljedicama (stenoza i/ili insuficijencija), neizbježno se nameće potreba da se i ovaj entitet uvrsti u raspravu o ALVT-u. Naš je, naime, pacijent imao uz opisane promjene i BAV s izrazitom patološkom dilatacijom ascendentne aorte, ali i velikih aortalnih ogranaka (brahiocefalički trunkus, lijeva zajednička karotidna arterija, lijeva potključna arterija). Ove su promjene opisivane u većine bolesnika s bikuspidalnom aortalnom valvulom koja se u odrasloj dobi opisuje pod pojmom „sindrom bikuspidalne aortalne valvule“ (sindrom BAV), uglavnom u okviru prirođenih srčanih grješaka koje se zajedničkim imenom nazivaju opstrukcijske lezije izlaznoga trakta lijeve klijetke (engl. *Left Ventricular Outflow Tract Obstruction Lesions* – LVOTOL). Spoznaje o vrijednosti bikuspidne aortalne valvule počele su se jasnije razabirati u razdoblju kada i aortoventrikulski tunel. Kod sindroma BAV mora se navesti njezina orijentacija ili tip (anteroposteriorna - tip I, lijevo-desna - tip II, korijenski ili *root fenotype* - tip III). U zahvaćene strukture sindroma BAV osim same valvule pripadaju aorta sa svim svojim segmentima; istmus aorte (zbog moguće pridružene koarktacije), subaortalna regija zbog mogućeg razvoja subaortalne stenoze, ali i mitralna valvula zbog razvoja sindroma Shone (20,21). Od osobite je važnosti dilatacija uzlazne aorte koja je posljedica već spomenutih cističnih promjena aortalne stijenke u bolesnika s ALVT-om (11), a kasnije temeljito opisane promjene u cijeloj aorti kod sindroma BAV (22). Vjerojatno je u istraživanje ovog rijetkog entiteta potrebno uključiti i genetički pristup koji je nadaleko uznapredovao upravo na razini istraživanja LVOTOL-a, zapravo najdalje u cijeloj molekularnogenetičkoj analizi prirođenih srčanih grješaka (23-25). U našem istraživanju međusobnog prožimanja srčanih lezija vezanih za BAV, a u okviru lezija izlaznoga trakta lijeve klijetke, predložili smo da se i u dječjoj dobi nalaz bikuspidalne aortalne valvule naziva sindromom bikuspidalne aortalne valvule kao što je to i u odrasloj dobi (26). Nema sumnje da bi i ovaj rijetki entitet koji se opisuje kao aortoventrikulski ili aorto-lijevo ventrikulski tunel valjalo uključiti u genetičke studije koje se odnose na poremećaje u izlaznom traktu lijeve klijetke (9,11,12,27-29). Neki autori navode da je incidencija ALVT-a u ukupnom broju prirođenih srčanih grešaka 0,03 % -0,46 % (4,11,30), ali neki autori navode samo 0,001 % (19). Prvi epidemiološki podatak javlja se 1982. godine i spominje samo 32 opisana slučaja (33), do 2002. godine opisano je 130 (8), a do 2018. oko 200 slučajeva (12). To znači da se godišnje ne objavljuje više od 5 slučajeva premda je učestalost pojave zacijelo ipak veća. Prema tim navodima, a uzimajući u obzir hrvatske epidemiološke studije (31,32), u Hrvatskoj bismo mogli očekivati jednog pacijenta s ALVT-om svakih 5-6 godina.

Dijagnostičke metode i mogućnosti fetalne kardiologije

Metoda izbora za dijagnozu ALVT-a jest dvodimenzijska i kolordoplerska ehokardiografija (4,8,14,15). Iz duge parasternalne osi može se u cijelosti prikazati tunel tako da se prati njegov tijek od aortalnog do ventrikulskog otvora. Pregledom protoka doplerom u boji može se pratiti gibanje kontrasta u sistoli i dijastoli, paravalvularno, a dodatnim pregledom iz kratke osi može se odrediti odnos tunela prema koronarnim kuspisima. K tome, neophodno je isključiti moguću stenozu izlaznog trakta desne klijetke koja se rijetko prikazuje kao posljedica ALVT-a. Sama se aortalna valvula može promatrati dodatno iz kratke osi, kako bi se isključila sumnja na moguću valvularnu stenozu, proširenje sinusa Valsalve, moguću displaziju aortalne valvule ili pridružen nalaz bikuspidne aortalne valvule s označenim tipom. Lijeva je klijetka u većine bolesnika značajno dilatirana, oslabljene sistoličke funkcije i moguće poremećene dijastoličke funkcije. Većina bolesnika ima dilataciju uzlazne aorte, a nekima je uzlazna aorta i dvostuko proširena (14). U našeg smo bolesnika, shodno prehodnim kriterijima, našli paravalvularni tunel promjera 4-5 mm koji se nalazi iznad desnog koronarnog kuspisa i doplerom u boji

se očituje insuficijencijom visokog stupnja koja seže do vrška lijeve klijetke, premda se ventrikulski otvor nalazi neposredno ispod aortalnog prstena. Sama lijeva klijetka je izrazito dilatirana i oslabljene sistoličke funkcije (EF 40 %). Ukupni stupanj insuficijencije pripada paravalvularnom tunelu (+++) u odnosu na minimalnu insuficijenciju bikuspidne aortalne valvule (+) anteroposteriorne orijentacije (nerazdvojeni koronarni kuspisi). Uzlazna aorta je bila dvostruko šira od normalnih vrijednosti, kako u fetalnoj tako i u ranoj postpartalnoj dobi (sl. 1 i 3). Rendgenska slika postpartalno potvrđuje kardiomegaliju i sumnju na dilataciju uzlazne aorte, ali je interpretacija vjerojatno ograničena velikim desnim režnjem timusa (sl 2). Najčešća zabluda ehokardiografije je diferencijalna dijagnoza ALVT-a prema ventrikulskom septalnom defektu koji se zamjenjuje s ventrikulskim ušćem ALVT-a (1,33,34), ali i insuficijencija aortalne valvule i ruptura aneurizme Valsalvinog sinusa (7,15). Druga metoda za točniju dijagnozu i diferencijalnu dijagnozu prema drugim, sličnim kanalima između aorte i ventrikula jest kateterizacija srca s angiokardiografijom. Uz razjašnjenje odnosa s koronarnim arterijama isključenje koronarnih fistula kao izoliranog fenomena ili pak komunikacija koronarnih arterija s ALVT-om, kateterizacijom se mogu izmjeriti tlakovi desne i lijeve strane srca, a dodatno se angiografskim prikazom isključuju pridružene hemodinamske ili morfološke promjene. Isključuje se opstrukcijska lezija izlaznog trakta desne klijetke, nalazi se najčešće povišen end-dijastolički tlak lijeve klijetke kao izraz poremećene dijastoličke funkcije, a nalazi se i divergentan tlak u aorti kao posljedica ALTV-a (1,3,8,11,15,35). Kod našeg smo bolesnika isključili stenozu izlaznoga trakta desne klijetke, pokazali visoki end-dijastolički tlak u lijevoj klijetki (16 mm Hg), prikazali dilataciju uzlazne aorte dvostukog promjera u odnosu na normalnu tubularnu aortu, ali smo prikazali i dilataciju aortalnih ogranaka, osobito brahiocefaličnog trunkusa. Isključena je insuficijencija ili/i stenoza aortalne valvule ili drugi entitet koji se opisuje kao mogući patološki kanal između korijena aorte i ventrikula (desnog ili lijevog) (sl. 5). U orijentaciji samog ALVT-a prema koronarnim kuspisima od veće je koristi bio ehokardiografski pregled. S obzirom da je primjena magnetske rezonancije remećena tehničkim problemima u ranoj novorođenačkoj dobi (8,16, 36), moguće je učiniti i MSCT koji pomaže u još jasnijem prikazu ukupne patologije (sl. 4).

Premda je većina bolesnika opisivana postpartalno, pa čak i u odrasloj dobi, s povećanjem senzitivnosti fetalne kardiologije sve se češće opisuju djeca u fetalnoj dobi. Sredinom 80-tih godina prošlog stoljeća senzitivnost fetalnog kardiološkog pregleda bila je u gestacijskoj dobi 18-22 tjedna samo 25 %, a u razdoblju od 1993. do 1995. s uvođenjem sagitalnih osi, uključujući i 3VV (presjek kroz tri krvne žile, engl. 3 *vesselview*) povećala na 40 %, a tek 2015. godine, zahvaljujući ukupom pregledu srca iz sagitalnih (3VVT, engl. *3 vessel and tracheaview*) i uzdužnih osi na različitim razinama postiže se senzitivnost više od 95 %. Iako i dalje postoje ograničenja (npr., smještaj fetusa i smještaj srca, multipla trudnoća, prematurno zatvaranje ovalnog otvora i Botallova duktusa, potpuni anomalni utok pulmonanih vena, koarktacija aorte, progresivna aortalna stenoza, heterotaksija i izomerizam), mislimo da se već od 2000. godine u rukama iskusnih pedijatrijskih kardiologa– fetologa može postaviti i dijagnoza ALVT-a. Ipak, rijetki opisi iz prenatalne dijagnoze mogu se naći od 1996. (Sousa-Uva) (15) i 2000 (Grab) (10), a do 2011. dokumentirano je samo 16 slučajeva prenatalno dijagnosticiranih ALVT (37,38). Osnovno obilježje prenatalnog ehokardiografskog pregleda je u prvom pristupu aortalna regurgitacija, a iz 4 chw gotovo uvijek dilatacija lijeve klijetke. Prikaz obojenim doplerom prikazuje turbulentnu regurgitaciju koja se može jasno prikazati pozornim promatranjem kao paravalvularna. Dodatni prikaz je gotovo redovito jasna dilatacija tubularne aorte (39). Kod našeg su bolesnika u cijelosti prisutni svi spomenuti kriteriji kako je navedeno, s dodatkom nalaza bikuspidalne aortalne valvule anteroposteriorne orijentacije. Tome valja dodati da su izračunati i sljedeći patološki parametri: indeks ventrikulske učinkovitosti ili Tei indeks (0,62), kardiovaskularni profil prema Huhtai bio je 4 (40), izmjerene su pozitivne pulsacije umbilikalne vene i venoznog duktusa (++) te ekstremna dilatacija tubularne aorte (18 mm – > 2 SD, iznad 95. percentile) (sl. 2,3,4,5). Ovdje navodimo samo parametre koji se danas mogu mjeriti već intrauterino kod drugih grješaka, a dosada nismo našli opisanih u prenatalnoj dijagnostici ALVT-a.

Klinički aspekti ALVT-a

Respektirajući moguće morfološke promjene kao i njihovo hemodinamsko značenje, u fetalnoj se dobi jamačno očekuje srčana insuficijencija (dilatacija i oslabljena kontraktilnost lijeve klijetke, smanjen CVPS, povećan CTI, pozitivne pulsacije DV i UV, što su bez daljnjega znakovi srčane insuficijencije), ali još bez hidropsa (8,9,12). Progresivna insuficijencija s pojavom hidropsa može dovesti intrauterino do letalnog ishoda, a također i do postpartalne maladaptacije s mogućim letalnim ishodom (15,38-41). Fetusi koji su umrli intrauterino zbog srčane insuficijencije popratnim hidropsom imali su CVPS u prosjeku 1,5 (40), a naš je pacijent imao 4. S obzirom da se ta vrijednost održavala od trenutka dijagnoze i da se nije pojavljivao hidrops, nismo uvodili intrauterinu terapiju srčane insuficijencije. Nije jasno bi li se intrauterina srčana insuficijencija kod ALVT-a trebala liječiti diureticima, digitalisom i ACE inhibitorima ili samo ACE inhibitorima i direticima, bez digitalisa, a smjernice o tome,

iz razumljivih razloga, ne postoje. Sličan opis kliničke slike nalazimo među ranim publikacijama ALVT-a (10) gdje je umjesto spomenutih vrijednosti fetalne cirkulacije prikazan povećani indeks otpora u umbilikalnoj arteriji (indeks otpora, engl. *resistence index* – RI) i normalan RI u u središnjoj cerebralnoj arteriji. Neposredno postpartalno nalazimo varijabilno sistoličko-dijastoličko strujanje nad cijelim prekordijem i „*pulsus celer et altus*" nad perifernim arterijama, u cijelosti povećano srce na rendgenskoj slici s dilatacijom uzlazne aorte i tipičnim nalazom elektrokardiograma (kakav je opisan i kod našeg bolesnika), iako je kod nekih bolesnika EKG opisan kao normalan (5). Tijek bolesti je različit, od rapidnog pogoršanja u novorođenačkoj i ranoj dojenačkoj dobi do sindroma iznenadne smrti (9,11,12,41), pa sve do otkrića grješke u odrasloj dobi (5,47,49,50). Ipak, većinom se bolest očituje progresijom simptoma u ranoj neonatalnoj dobi ili najkasnije do završetka dojenačke dobi, pa je iz tih iskustava jasno da grješku treba što je moguće prije otkloniti. S obzirom da je kod našeg bolesnika napredovala srčana insuficijencija u neonatalnoj dobi, to smo nakon potpune laboratorijske obrade i potvrde dijagnoze te isključenja drugih, moguće pridruženih anomalija, uputili dijete na kardiokiruršku korekciju koja je i učinjena 16. dana života, dakle u ranoj neonatalnoj dobi postavljanjem autolognog perikardijskog *patcha* na mjesto ušća na aortalnoj strani (sinotubularni spoj).

Važnost ranog kirurškog liječenja i dostupne studije ishoda

Većina autora opisuje zatvaranje ALVT-a stavljanjem *patcha* na aortni ili/i ventrikulski otvor (4,6,13-15,42,43). Kod pacijenata kod kojih je zahvat učinjen u prvih 6 mjeseci života može se pratiti postupna normalizacija veličine i funkcije lijeve klijetke (13,43). Našeg smo pacijenta uputili na operaciju u ranoj neonatalnoj dobi čim smo zabilježili kliničke znakove srčane insuficijencije. Tako rani zahvat vjerojatno je i rezultirao odličnim postoperacijskim tijekom bolesti, postupnim oporavkom bez komplikacija i odličnim razvojem tijekom prve godine života. Kao glavne postoperacijske komplikacije javljaju se ostatni tunel i aortalna insuficijencija (19). S obzirom na prožimanje ALVT-a s patologijom same aortalne valvule (stenoza i/ili insuficijencija) te diferencijalno-dijagnostičkih problema prema drugim pridruženim anomalijama (koronarne arterije, izlazni trakt desne klijetke), postoje i modifikacije prilagođene tim stanjima. U 50 % slučajeva potrebna je zamjena aortalne valvule (3,6,42-45). Zatvaranje defekta intervencijski može se pokušati Amplatzerovim umetkom koji je inače namijenjen za zatvaranje muskularnog VSD-a (16,19). Napretkom dijagnostičkih i kardiokirurških metoda te sve dubljom spoznajom ALVT-a u odnosu prema moguće pridruženim ili čak etiopatogenetski srodnih grješaka otvaraju se nove perspektive u liječenju aorto-lijevo ventrikulskog tunela. Višegodišnjim praćenjem operiranih pacijenata u nekoliko studija je opisana značajnija aortalna insuficijencija i rekurentni aortoventrikulski tunel (11,51). Ostatni ili rekurentni ALVT je prepoznata komplikacija nakon kirurške korekcije koja se može javiti zbog odvajanja šavova. Pravo vrijeme i metode reoperacije ovih komplikacija izazov su za kirurge zbog dilatacije uzlazne aorte i progresije u aneurizmu u odrasloj dobi. Upravo je transkatetersko zatvaranje rezidualnog tunela sigurna i uspješna metoda kirurškog liječenja takvih pacijenata. U nekim slučajevima učinjena je zamjena uzlazne aorte da bi se spriječila ruptura aorte ili disekcija (44,46-48).

ZAKLJUČAK

Aorto-lijevo ventrikulski tunel je izrazito rijetka, ali izliječiva prirođena srčana grješka koja se može dijagnosticirati već u fetalnoj dobi zahvaljujući u prvom redu ehokardiografskoj analizi doplerom u boji. Etiopatogenetski se može svrstati u grješke slične sindromu bikuspidalne aortalne valvule, a hemodinamski se očituje kao teška paravalvularna insuficijencija aortalnog ušća s moguće pridruženim manje ili više hemodinamski značajnim anomalijama. Ako se greška otkloni kirurškim putem prije nego nastupi srčana insuficijencija, izliječenje je potpuno, ali i dalje bolesnika treba kontrolirati zbog najčešće pridružene patološke dilatacije uzlazne aorte.

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SUMMARY

AORTO-LEFT VENTRICULAR TUNNEL – FETAL DIAGNOSIS AND EARLY NEONATAL TREATMENT AS A PRECONDITION FOR SUCCESFUL DISEASE OUTCOME

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We present a patient with aorto-left ventricular tunnel (ALVT) diagnosed in the gestational age (GA) of 27 weeks. Examination was indicated by an obstetrician due to cardiomegaly. ALVT manifested itself by an extreme dilatation of the left ventricle (LVIDd 32 mm, >2 SD), a significantly decreased contractile ability (ejection fraction (EF) 40%) and color Doppler display of an asymmetric aortic valve insufficiency via a canal flowing from the sinotubular junction to the left ventricle, between the interventricular septum and subinfundibular portion of the right ventricle. Myocardial performance index was 0.62 (normal 0.25-0-50), cardiovascular profile score 4 (normal 10), a-wave in ductus venosus (DV) positive (++) (as positive evidence for fetal cardiac dysfunction) and positive umbilical venous pulsations. In addition, an extremely dilated tubular aorta was also found (18 mm – >2 SD, above 95th percentile). In that gestational age, aortic valve ring was measured 5.8 mm (75th percentile), and the width of extravalvular tunnel 4-5 mm. Since no hydrops was found, in utero treatment with medicines was not used. Cardiomegaly was found postpartum (x-ray), and the ALVT diagnosis was confirmed by echocardiography. The canal was located above the right coronary cusp, i.e. in front of the raphe connecting the left and right coronary cusp, meaning that the diagnosis of a bicuspid aortic valve (BAV) of anterior-posterior orientation was also made. Inotropic and diuretic therapy was ordered due to cardiac insufficiency development. Diagnosis was also confirmed with multi-slice computed tomography and heart catheterization (angiocardiography). Cardiac surgery was performed at the age of 16 days by placing an autologous pericardial patch on the aortic canal opening. Diuretic, digitalis and angiotensin-converting enzyme inhibitor were ordered postnatally. Left ventricle was recovering incrementally (3 months after surgery, EF 50%), but pathological dilatation of tubular aorta persisted. Complete recovery of the left ventricle is expected, with the need for further observation of the patient because of the BAV and possible effects on the valve itself and on the ascending aorta. At the age of 10 months, contractility of the left ventricle was normal (EF 65%), with mild aortic insufficiency (central), normal flow through the aortic valve, but dilatation of the ascending aorta persisted (ascending aorta width 2.1 cm, >2 SD).

Key words: aorto-left ventricular tunnel, prenatal diagnosis, cardiac insufficiency, early cardiosurgical therapy, fetal cardiology, rare diseases

STOOL-NEGATIVE NON-THYPHOIDAL *SALMONELLA* URINARY TRACT INFECTION: EXTREMELY RARE, YET STILL POSSIBLE CAUSE OF URINARY TRACT INFECTION IN KIDNEY TRANSPLANT RECIPIENTS

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Non-thyphoidal *Salmonella* usually presents as gastroenteritis while extra-intestinal manifestations are rare and mostly occur in patients with predisposing conditions such as chronic illness, urinary tract abnormalities, and immunosuppression. Urinary tract infection is the most common infectious complication in kidney transplant recipients. There are very few cases of urinary tract infections caused by non-thyphoidal *Salmonella* in kidney transplant recipients in the English literature, and to the best of our knowledge, only nine cases being stool negative. Although being extremely rare, non-thyphoidal *Salmonella* should be considered as one of the possible causes of urinary tract infections in kidney transplant recipients even without concomitant or preceding gastrointestinal symptoms. Bacteriuria can be present for some time after treatment requiring prolonged treatment and urine culture surveillance.

Key words: non-thyphoidal Salmonella, urinary tract infection, kidney transplantation

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INTRODUCTION

Urinary tract infection (UTI) is the most common infectious complication in kidney transplant recipients with the incidence of 25%-75%. Gram-negative bacteria account for more than 70% of all UTI in kidney transplant recipients, with *Escherichia coli* being the most common pathogen followed by *Klebsiella* spp., *Pseudomonas aeruginosa* and *Enterococcus* spp. with significantly increasing rate of multidrug resistant pathogens (1, 2). Non-typhoidal *Salmonella* (NTS) urinary tract infection is rather uncommon and usually occurs in patients with predisposing conditions (3, 4). There are very few cases of NTS urinary tract infections in kidney transplant recipients in the English literature, and to the best of our knowledge, only nine cases being stool negative. We bring a case of our kidney transplant recipient with stool negative NTS UTI, with review of the literature.

CASE REPORT

At the age of 47, our patient with polycystic kidney disease received kidney from a deceased donor after previously having been treated with hemodialysis for 7 years. She received basiliximab as induction immunosuppressive therapy, followed by tacrolimus, mycofenolate-mofetil and steroids. Early posttransplant course was complicated with culture proven urinary tract infection caused by *Enterococcus faecium* and *Escherichia coli*. She was successfully treated according to the antibiotic sensitivity report and discharged from the hospital with excellent graft function. Subsequent posttransplant course was uneventful with no episodes of urinary tract infections. Graft function remained excellent with no episodes of acute rejections. Six years after transplantation, the patient presented to emergency room with fever and dysuria. No symptoms of gastrointestinal illness were present whatso-

ever. Laboratory investigations found increased white blood count and elevated C-reactive protein. Urine culture showed significant growth of *Salmonella enterica* Group B while stool samples and blood cultures remained negative. She was treated with ciprofloxacin 500 mg twice daily for 14 days with excellent clinical response. Repeated urine culture after treatment were sterile and graft function remained stable.

DISCUSSION

Non-typhoidal *Salmonella* (NTS) infections usually present as gastroenteritis, while extra-intestinal presentation is much less frequent and occurs mostly in immunocompromised patients (3,5,6). NTS urinary tract infections are uncommon with the occurrence frequency in the reported studies ranging from 0.015% to 0.9% (4,7,8), although one study has reported a higher prevalence of 3.4% (9). Infections are mainly associated with predisposing conditions such as chronic illness, immunosuppression or underlying urinary tract abnormalities (3,4,7). There are only few cases of NTS UTI in kidney transplant recipients reported in the English literature to date. Ramos *et al*. report the largest series of 7 patients. Urine culture was positive in all of them, with four patients having clinical manifestation of UTI and 3 patients having bacteremia with bacteriuria. Stool sample was positive in 3 patients, two of them having bacteremia. In 2 patients with negative stool and blood samples, bacteriuria was present after treatment for 5 and 8 weeks, respectively and they required prolonged treatment (10). In the report by Mussche *et al*., in 3 of 4 patients with NTS UTI stool samples were negative, two patients having bacteremia (11). Allerberger *et al*. report on 5 patients, 4 of them being positive for NTS in urine and stool samples while one patient was not tested for stool specimen. In 3 patients, asymptomatic bacteriuria was present after treatment for 3 weeks, 16 months and 13 months, respectively, with the latter patient developing NTS bacteriuria after 6 months of persistent bacteriuria (7). Two studies of 20 and 19 patients with NTS UTI report one kidney transplant recipient each. While Mellon *et al*. report on a patient with positive finding of NTS in stool samples, as well in blood cultures, Tena *et al*. report on a patient with negative stool, as well as blood samples (4, 12). In a single case report, Ito *et al*. describe a kidney transplant recipient with stool negative NTS UTI (13).

CONCLUSION

Non-thypoidal *Salmonella* is an extremely rare but possible cause of UTI in kidney transplant recipients. It should be considered as one of the possible causes of UTI in kidney transplant recipients even without concomitant or previous gastrointestinal symptoms. Bacteriuria can be present for some time after treatment requiring prolonged treatment and urine culture surveillance.

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SAŽETAK

INFEKCIJA MOKRAĆNIH PUTOVA UZROKOVANA NETIFOIDNOM SALMONELOM UZ NEGATIVAN NALAZ KOPROKULTURE – NETIFOIDNA SALMONELA: IZNIMNO RIJEDAK, ALI MOGUĆ UZROK INFEKCIJE MOKRAĆNIH PUTOVA U BOLESNIKA S TRANSPLANTIRANIM BUBREGOM

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Gastroenteritis je najčešća posljedica infekcije netifoidnom salmonelom. Ekstraintestinalne manifestacije su iznimno rijetke i najčešće se viđaju u bolesnika s predisponirajućim stanjima kao što su kronične bolesti, bolesti urotrakta i stanja povezana s imunosupresijom. Infekcije mokraćnih putova su najčešća infektivna komplikacija u bolesnika s transplantiranim bubregom. U literaturi je do sada opisano svega nekoliko slučajeva infekcija mokraćnih putova uzrokovanih netifoidnom salmonelom, a u samo devet slučajeva bakterija nije dokazana i u uzorcima stolice. Netifoidna salmonela je iznimno rijedak, no moguć uzročnik infekcija mokraćnih putova u bolesnika s transplantiranim bubregom, čak i u slučajevima bez pridružene ili prethodne kliničke slike gastroenteritisa. Nakon provedenog liječenja može zaostati asimptomatska bakteriurija pa je nakon završetka liječenja potrebno redovito uzimati nadzorne urinokulture.

Ključne riječi: **netifoidna salmonela, infekcija mokraćnih putova, transplantacija bubrega**

PREVALENCE OF SMOKING IN CROATIA – HOW TO SOLVE THE PROBLEM?

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Tobacco use is the leading preventable cause of death, which is why a number of measures to reduce its use are carried out in the world. The purpose of this paper is to highlight the indicators related to the use of tobacco products in Croatia, as well as possible solutions within the framework of existing and proposed policies against tobacco. We have used data collected in the EU countries in 2016, according to which the prevalence of smoking in Croatia is among the highest in Europe. In order to reduce the prevalence of smoking and improve the health of its population, Croatia needs to strengthen and adopt additional policies on tobacco control.

Key words: smoking, prevalence, tobacco policies, Croatia

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INTRODUCTION

During the 20th century, the consumption of tobacco has grown to an epidemic with far-reaching medical consequences. Along with many other factors, development of the tobacco industry has been the leading cause of that epidemic (1).

The morbidity and mortality caused by the consumption of tobacco are the result of many complex interactions in the human body. Tobacco smoke is known to contain over 4,000 different chemical compounds. Exposure to tobacco smoke in closed spaces is harmful to everyone, smokers and non-smokers alike, and can be the cause of disease of almost every organ of the human body (1).

Smoking is also a risk factor for major non-contagious diseases, heart diseases, stroke, malignant diseases, diabetes and chronic obstructive pulmonary diseases (2). It has been connected to six out of eight leading mortality causes in the world (3). According to the World Health Organization (WHO), the tobacco epidemic of the 20th century is responsible for death of around 100 million people around the world, and if urgent measures are not taken soon, that number might grow to one billion in the 21st century (4). It is assumed that these numbers are even higher, given that only certain diseases were considered, and the research shows ever more diseases to be connected to smoking (1). Smoking also affects the economy; the financial losses associated with medical consequences of smoking are enormous. It is estimated that the European Union (EU) spends around 25 billion € on medical treatments of the diseases caused by smoking (5).

Given that smoking is the highest avoidable health risk in Europe, and in the developed world in general, causing more problems than alcohol, drugs, high blood pressure, obesity or high cholesterol levels, the governments' efforts around the world to decrease the prevalence of smoking are intensive (6). During the last few decades, the programs in certain countries have shown significant results. During the 2000-2010 period, the prevalence of smoking among adults (15 years of age and above) was decreased by 37.6% in Iceland and by 40.6% in Norway (7). In addition, some

countries have set a high goal to eliminate or reduce the prevalence of smoking almost to zero in a very short period of time. New Zealand aims to eliminate the usage of tobacco completely by the year 2025 (8), whereas Finland aims to achieve that goal by the year 2040 (9).

While the prevalence of smoking is decreasing in many developed countries such as Australia, New Zealand, United Kingdom, Canada and USA, in some countries such as developing countries, countries of Southern, Central and Eastern Europe, including Croatia, the prevalence is still growing, or does not show any changes (2).

Therefore, the aim of this study was to highlight the indicators related to the use of tobacco products in Croatia, as well as the possible solutions within the framework of the existing and proposed anti-tobacco policies.

RECENT EVIDENCE ON SMOKING TRENDS IN CROATIA

To show the current pattern of tobacco use in Croatia, this study used the selected data from a survey conducted in 2016 in the EU countries, in which Croatia participated as a member state for the second time (5). The survey was carried out by the TNS Opinion & Social network. A total of 27,901 respondents from different social and demographic groups were interviewed face-to-face at home in their mother tongue. The methodology used was that of Eurobarometer and survey is described in the Special Eurobarometer 458 report (5).

Prevalence of smoking in Croatia

The prevalence of smoking shows the amount of smokers in a certain country, and helps shape the policies against smoking. According to the research conducted in the EU in 2016, 35% of the adults in Croatia are smokers, which is the third highest prevalence of smoking in the EU, right behind 37% in Greece and 36% in Bulgaria and France (Table 1). In addition, the prevalence of smoking in Croatia is higher among men than women (38% *vs*. 32%), while the EU average is 30% *vs*. 22% (5).

The amount of people that have never smoked is 49% in Croatia, less than the average in the EU (Table 1), while the amount of people that have quit smoking is 16%, amongst lowest in the EU, right behind Bulgaria (13%), Hungary, Italy, Portugal and Romania (14%) (Table 1).

In Croatia just as in almost all EU member countries, apart from Sweden, more than 9 out of 10 smokers use tobacco products on everyday basis, usually packed cigarettes (above 79%) (5).

Croatians smoke a mean of 17.9 cigarettes a day, which is a bit less than in Austria (18.4) and Cyprus (18.9), the countries with the highest smoker ratio in the EU (Table 1).

Table 1.
Prevalence of smoking in the European Union and number of cigarettes smoked per day. (%; mean + evolution compared with EB82.4 2014.). Source: European Commission. Attitudes of Europeans towards Tobacco and Electronic Cigarettes: special Eurobarometer 458. Brussels: EC, 2017. doi: 10.2875/804491

Country	Smoking prevalence		Never smoked		Ex-smokers		Cigarettes *per* day*	
	%	2017 - 2014	%	2017-2014	%	2017 - 2014	Mean	2017-2014
Greece	37	↓1	44	=	19	↑1	17.8	↓1.8
Bulgaria	36	↑1	51	↑2	13	↓3	15.9	↑0.1
France	36	↑4	42	↓4	22	=	12.6	↓0.6
Croatia	**35**	↑2	**49**	↓2	**16**	**=**	**17.9**	**↑0.8**
Latvia	32	↑2	45	↓4	23	↑2	11.5	↓1.3
Poland	30	↑2	52	↓4	18	↑3	15.9	↑0.2
Czech Republic	29	↑4	52	↓5	19	↑1	15.4	↑0.6
Lithuania	29	↑3	53	↓3	18	=	12.2	↓0.4
Republic of Cyprus	28	↓3	55	↑1	17	↑2	18.9	↓0.6
Austria	28	↑2	53	↓4	19	↑2	18.4	↓1.7
Romania	28	↑1	58	↓2	14	↑1	15.7	↑1.2
Slovenia	28	↓2	53	↑1	19	↑1	15.7	↓1.6
Spain	28	↓1	50	↓2	22	↑3	11.7	↓2.2
Hungary	27	↓3	59	↑1	14	↑3	16.3	↓0.2

Table 1. - continued

Portugal	26	↑1	60	↓3	14	↑2	13.2	↓1.9
Slovakia	26	↑5	57	↓6	17	↑1	15.9	↑2.8
Germany	25	↓2	52	↑2	21	↓1	15.2	↓0.4
Malta	24	↑4	57	↓4	19	=	17.0	↑1.4
Italy	24	↑3	62	↓1	14	↓2	13.6	↑0.4
Estonia	23	↑1	53	↓3	24	↑3	13.2	↑1.3
Luxembourg	21	=	57	=	22	=	14.8	↑1.6
Finland	20	↑1	51	↓6	29	↑5	12.7	↓1.2
Belgium	19	↓6	57	↑1	24	↑5	13.8	↓0.8
Denmark	19	↓4	48	↑1	33	↑3	13.7	↓0.1
Ireland	19	↓2	63	↑4	18	↓1	13.8	↓0.7
The Netherlands	19	↓4	49	↑3	32	↑1	12.6	↑0.9
United Kingdom	17	↓5	60	↑1	22	↑3	12.4	↓2.3
Sweden	7	↓4	52	↓1	41	↑6	10.4	↓1.3
EU28	**26**	**=**	**53**	**↓1**	**20**	**=**	**14.1**	**↓0.6**

*Base respondents who smoke cigarettes daily, N=6,741

Exposure to tobacco smoke in public places

More than half (77%) subjects in Croatia said that they had been exposed to tobacco smoke when visiting bars (Table 2). This is significantly higher than the EU average (25%) (Table 2). In contrast, only 2% of the subjects in Sweden, 5% in the UK, and 6% in Slovenia and Ireland said so (Table 2).

Table 2.
Exposure to tobacco smoke in public places, a drinking establishment such as a bar (% + evolution compared with EB82.4 2014.). Source: European Commission. Attitudes of Europeans towards Tobacco and Electronic Cigarettes: special Eurobarometer 458. Brussels: EC, 2017. doi: 10.2875/804491

	A drinking establishment such as a bar	2017-2014
Greece	87%	↑4
Croatia	**77%**	↓1
Czech Republic	73%	↓10
Republic of Cyprus	65%	↓9
Austria	57%	↓17
Slovakia	50%	↓7
Bulgaria	42%	↑5
Malta	39%	↓10
Denmark	39%	↓4
Portugal	38%	↓5
Germany	22%	↓7
Latvia	22%	↓6
The Netherlands	20%	↓11
Belgium	18%	↓5
France	16%	↓2
Italy	15%	↑2
Poland	14%	↓7
Spain	12%	↓5
Romania	11%	↓69
Luxembourg	11%	↑3
Estonia	11%	↓5
Lithuania	11%	↓7
Finland	7%	↓1
Hungary	7%	↓2
Ireland	6%	↑1
Slovenia	6%	=
United Kingdom	5%	↓1
Sweden	2%	=
EU28	**25%**	**↓5**

Starting/stopping smoking tobacco

Croats begin smoking regularly at the mean age of 17.9 years, and every other smoker tried to quit smoking at some point in their life (5). In doing so, the majority (85%) of them tried to quit smoking (and some managed to quit) without help, 3% used nicotine substitutes (patches, etc.), the same number had support from their doctors or other health professionals, and 5% used electronic (e)-cigarettes or similar products (5).

Awareness and attitudes towards the use of e-cigarettes

In Croatia, 11% of respondents were using e-cigarettes. None is currently using them, 1% used them briefly, while 10% tried but never used them regularly (5). In general, in this research, the most common reason for switching to e-cigarettes was a desire to reduce or stop smoking (61%). About one-third (31%) say that they

started using e-cigarettes because they considered them less harmful than tobacco. An additional factor for the usage of e-cigarettes was their use in the places where 'regular' smoking was not allowed (15%) (5). Older respondents who use e-cigarettes reported that they most commonly used those containing nicotine (5).

In all EU member states, smokers and former smokers who have tried or used e-cigarettes usually say that their tobacco smoking is not reduced as a result of using e-cigarettes (5). Thus, in Croatia, more than half (76%) of the subjects have not reduced their smoking by using e-cigarettes; on the contrary, 10% of them increased their consumption of tobacco (5). More than half of all subjects in the EU believe that e-cigarettes are harmful (55%), and Croats seem to have the same opinion (51%) (5).

HOW TO SOLVE THE PROBLEM?

The prevalence of smoking in Croatia is among the highest in Europe (5), and according to the WHO estimate, if these trends continue, the situation will not change significantly in the next ten years (11). That is to say, if Croatia does not adopt the global objective of reducing tobacco consumption by 30% by 2025, this goal will not be reached despite the measures taken so far (11).

To put it simply, reducing the prevalence of smoking could be achieved by prohibiting the sale of tobacco, which is not surprising given the fact that the harmful effects of tobacco on human health have been evidenced for more than half a century (12). The sale of tobacco is currently only entirely banned in Bhutan, although the desired success in the absolute elimination of tobacco use has not been achieved, which suggests that regulation is still a more preferable measure than prohibition, a measure which proved to be a bad example already in the 1930s (13,14). In addition to the fact that the tobacco industry is currently one of the strongest and most influential industries in the world, including Croatia, which has a long tradition in the production of tobacco products and a strong and promising national industry, this legal possibility, however, should be replaced by other, more appropriate measures. For example, California state legislators and staff expressed greater interest in annual reduction in licenses of tobacco retailers *versus* total sale ban. Similarly, Finland has decided to increase the fee for retail license, as specified in the Finland 2016 Tobacco Act. Regulation of the retail environment is a likely indicator of achieving an endgame goal (15).

Therefore, other legal options should be considered, particularly those regulating smokeless environment. One of the measures would certainly be ban on smoking in public places, which could, among other things, have a significant impact on denormalizing smoking in the community. The ban on smoking affects the behavior of the general population by reducing opportunities and increasing social non-acceptance of smoking. It also reduces the exposure of children to negative influences of the social pattern of behavior, which was the reason for the ban on smoking in parks and other public places in New York a few years ago (16). In 2008, the law on banning smoking from the public areas was adopted in Croatia (17). However, under the pressure from the tobacco lobby, the law was soon amended. Smoking is permitted in bars in separate zones, while restaurants must have a separate area for smokers where food and drink are not served. Catering facilities smaller than 50 m^2 can be determined as a smoking area in its entirety (18). In this research, the majority of Croats (77%) said they had been exposed to tobacco smoke during their visits to bars, and the amount of exposure to smoke in bars is considered to be an indicator of success in implementing the anti-smoke policies (16). When this kind of legislation was proposed in Ireland, the tobacco industry also strongly argued that smoking was an integral part of the pub culture of the country and that the ban would be impossible to achieve and cause an irreparable economic damage to the owners of pubs (19). Yet, now the country has been smoke-free for several years, with strong public support and no negative impact on the business (19,20). Ireland provides strong evidence for the positive health effects of no-smoke environment, and researches in other countries also confirm the beneficial health effects of these policies. Thus, after the introduction of measures to reduce exposure to secondhand smoke, the number of admissions for acute coronary syndrome has also been reduced (21). In order to achieve the implementation of these measures, which requires appropriate amendments to the existing legislation, Croatia should follow the WHO recommendations, the step by step process, as the most effective method to achieve a smoke-free environment (22).

Most tobacco users start smoking at an early age, as confirmed by the research presented in the EU countries. Smoking habits are usually created and adopted at a teen age, which indicates that preventive programs directed towards young people should have a key role in reducing the prevalence of smoking (1). In addition, children are particularly vulnerable to the negative effects of either active or passive smoking, become quickly addicted to tobacco, and the earlier they start smoking the harder it is to quit later in life. Therefore, the initiative of Singaporean scientists to ban the sale of tobacco to those born in 2000 and later seems reasonable (23). Although some authors consider

this proposal unconvincing (24), it is still less likely for people who have not started smoking at an earlier age to start smoking at an older age, the age when according to the said proposal they will be no longer forbidden to purchase tobacco products. The potential effective measures to reduce the initiation of smoking among young people could include reducing the number of stores for sale of tobacco. By decreasing the number of places where tobacco is sold, restricting the access to young people to these places, not allowing the sale of tobacco products in stores near schools, the perception of tobacco as an abnormal product shall be reinforced, while tobacco products shall be less available (25).

There are many factors that influence the choice of a particular brand of cigarettes, and among the most common are its price and taste. It is believed that an increase of taxes on tobacco products is the most effective way of reducing the prevalence of smoking (26,27). Extensive researches have shown that higher taxes on tobacco products can help promote cessation among current users, deter initiation among potential users, and reduce tobacco use among those who remain users (28). Increasing the price of tobacco tends to decrease the prevalence of smoking among young people and adults, to which middle- and low-income countries are particularly sensitive (29). A survey conducted in 2010 in 20 lower/middle-income countries claimed that an increase in price by 10% reduced consumption among young people by 18%, which is a three times higher rate than among adults (30). Studies have also shown that changes in the relative prices of tobacco products can cause some users of tobacco to switch to the use of less expensive products (28). However, due to the belief that all tobacco products are seriously harmful to health, all products should be taxed similarly. For years, almost all EU countries have raised taxes on tobacco products, including Croatia, where this measure is one of the most important. However, the taxes are different, as well as the costs of cigarette pack in certain EU countries, and other countries. According to the 2016 report, tobacco prices in Croatia are among the lowest in EU countries (cigarette weighted average retail price was 3 € in 2016). Cigarettes are most expensive in Ireland (9.42 €) and cheapest in Bulgaria (2.42 €) (31). Cigarette prices are even lower in non-EU countries (e.g., Serbia, Bosnia and Herzegovina). All this creates the preconditions for purchasing tobacco products in the 'neighborhood' and illegal trading, which indicates that the prices of tobacco products in the region should not vary (6).

This survey also showed that around half of regular smokers smoke cigarettes with special characteristics. Interestingly, the observation of the tobacco industry in the survey on the attitudes of its customers shows that long-time users do not want to use cigarettes with low nicotine levels (32). Therefore, Peters considers that with the implementation of other necessary measures, "only the elimination of a tolerable, addictive cigarette will truly address the harms of smoking and the most vulnerable groups and is the cheapest, effective action as the full costs are transferred to the tobacco manufacturer" (24).

Additionally, there is a lot of evidence showing that cigarette packaging, including box format (size, shape, opening), color, logo and descriptors affect the perception of the health risks of smoking, the claim and attitudes towards smoking (33,34). Due to the increasing restrictions on tobacco advertising and marketing, in many countries, and in Croatia as well, cigarette packaging has become a key promotional medium of the tobacco industry (33,34). Therefore, today, the plain packaging is considered to be part of the entire public health strategy that aims to eliminate the morbidity and mortality caused by the use of tobacco (35,36), primarily by reducing the number of new, young smokers, and by promoting quitting amongst current smokers. Recently, after the implementation of measures of plain packaging of cigarettes, the Ministry of Health in Australia presented information on reducing the use of cigarettes. Cigarette sales declined in 2013 by 3% compared to 2012, and the amount of everyday smokers (14 years and older) decreased from 15.1% in 2010 to 12.8% in 2013 (37). Although these changes are not directly attributable just to plain packaging, they, however, suggest that the plain packaging contributes to the reduction of smoking at the population level (33). Warnings about the harmful effects of tobacco are placed on cigarette packs in Croatia, and according to the revised Tobacco Products Directive, those warnings feature pictorial health warnings as well (38).

The majority of smokers want to quit (85% plans to, and 50% actually tries to quit every year), but only the minority manages to quit (4%-6%) (39), which has also been confirmed by the study according to which every other smoker in Croatia has tried to quit. The interventions that have helped smokers quit smoking are considered to be among the most efficient, cost-effective medicine procedures. Roughly, after 35 years of age, every year of smoking reduces life expectancy by three months, and smoking cessation makes up most of this loss (40). In order to restrict access to tobacco products and encourage smoking cessation, Chapman proposed a smart card license for smokers, whose key feature is daily limit (41). With the proposal of such measures, the costs of treatment and pharmacological therapy should be covered for those people who wish to stop smoking. These procedures already exist in a number of EU countries (42), but unfortunately, not in

Croatia. For that reason, deficiencies in smoking cessation services were regarded by many as the greatest challenge to Tobacco-Free Finland 2030 (15).

E-cigarettes are a product that appeared a few years ago and attitudes towards them are contradictory. While some see e-cigarettes as a potential tool to quit smoking (43), to others they represent a health hazard by encouraging adolescents to start smoking conventional tobacco products (44). Some, however, see e-cigarettes as a means of the tobacco industry to create new marketing opportunities (45). Respondents in Croatia said that their use of e-cigarettes helped neither quit nor reduce tobacco use, and they resorted to them in places where tobacco smoking was not allowed, which is consistent with the observation that with the use of e-cigarettes, smokers actually become dual smokers, smokers who smoke both standard tobacco and e-cigarettes (43). Furthermore, in accordance with the expected social non-acceptance of tobacco use and consequent marginalization of smoking, it is reasonable to suspect that the e-cigarettes could replace the classic tobacco products, and that there is a need for appropriate regulation and measures to prevent their use by those who have never smoked (especially children), to protect non-users, to maximize their effectiveness as an aid to quit smoking and discourage their dual use for a longer period (46).

CONCLUSION

In order to decrease the prevalence of smoking and to improve the health of its citizens, Croatia should strengthen the current tobacco control policy, and adopt certain other policies. The successful experiences of other countries that have managed to decrease the prevalence of smoking have shown that only the integrated approach can be completely effective. Comprehensive approach should include effective policies for tobacco control such as raise taxes on tobacco products, protect people from tobacco smoke, warn about the dangers of tobacco, enforce bans on tobacco advertising, promotion and sponsorship, and offer help to quit tobacco use, which is a key element of the WHO Framework Convention on Tobacco Control.

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SAŽETAK

UČESTALOST PUŠENJA U HRVATSKOJ – KAKO RIJEŠITI PROBLEM?

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Uživanje duhana vodeći je preventabilni uzrok smrtnosti zbog čega se u svijetu provode brojne mjere kako bi se smanjila njegova uporaba. Stoga je cilj ovoga rada prikazati pokazatelje vezane za korištenje duhanskih proizvoda u Hrvatskoj kao i moguća rješenja u okviru postojećih i predloženih protuduhanskih politika. U prikazu su korišteni odabrani podatci ankete provedene u zemljama Europske unije 2016. godine prema kojoj je učestalost pušenja u Hrvatskoj među najvišima u Europi. Kako bi smanjila učestalost pušenja i unaprijedila zdravlje svoga stanovništva Hrvatska treba ojačati postojeće i usvojiti dodatne politike o kontroli duhana.

Ključne riječi: **pušenje, učestalost, protuduhanske politike, Hrvatska**

KRANIOCEREBRALNE I MAKSILOFACIJALNE OZLJEDE LIJEČENE U ZAKLADNOJ BOLNICI REBRO U ZAGREBU 1942. – 1945.

DUBRAVKO HABEK i MARINA TOT

Hrvatsko katoličko sveučilište u Zagrebu, Zagreb, Hrvatska

U ovom su radu prikazani neistraženi podatci o bolesnicima s mirnodopskim i ratnim kraniocerebralnim i maksilofacijalnim ozljedama hospitaliziranima u Zakladnoj bolnici na Rebru u Zagrebu 1942.-1945. Hospitalizirano je 1532 pacijenata od čega s kraniocerebralnim ozljedama 964 (62,93 %), a s maksilofacijalnim ozljedama 568 (37 %). Prosječna dob zaprimljenih pacijenata bila je 30,19 godina, muškoga spola od 84 %, što ukazuje na pripadnost vojnim postrojbama mlađih dobnih skupina muškaraca. Najčešće prijamne dijagnoze bile su *Fractura mandibulae* (29,2 %), *Commotio cerebri* (23,3 %) i *Vulnus sclopetarium capitis* (19,3 %). Izliječeno je 7,0 % zaprimljenih, poboljšano zdravstveno stanje pri otpustu imalo je 80,6 %, neizliječeno je bilo 2,6 %, a umrlo je 9,1 % hospitaliziranih pacijenata. Najveći broj umrlih zabilježen je zbog dijagnoze *Commotio cerebri* (45 %), potom *Vulnus sclopetarium capitis* (25 %), a slijede *Fractura baseos cranii* i *Fractura cranii.*

Ključne riječi: kraniocerebralne ozljede, maksilofacijalne ozljede, II. svjetski rat, Hrvatska, bolnica Rebro, Zagreb

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UVOD

Zakladna bolnica Rebro u Zagrebu, jedna od malobrojnih novosagrađenih bolnica u Europi tijekom II. svjetskog rata, otvorena je 12. travnja 1942. godine. Uz postojeće Bolnicu Sestara milosrdnica, Zakladnu bolnicu na Svetome Duhu i Merkurov sanatorij te Kirušku kliniku Medicinskog fakulteta Zagreb, koje su imale kirurške odjele i zbrinjavale kraniocerebralne i maksilofacijalne ozljede u okvirima ondašnje opće kirurgije i otorinolaringologije, otvoreni su istovrsni odjeli u novoj Zakladnoj bolnici na Rebru. Ravnatelj bolnice bio je kirurg dr. Šime Cvitanović, šef kirurgije prim. dr. Mario Duić s kirurginjom dr. Ljubicom Bosner te šef odjela otorinolaringologije dr. Baldo Dukić, a zdravstvenu njegu u bolnici obavljalo je 100 časnih sestara Svetoga križa u suvremenoj i novoj bolnici sa cjelovitom opremom i svim potrebnim logističkim sadržajima. Kirurški odjel sa 119 kreveta i 6 operacijskih dvorana bio je smješten na II. katu, a odjel za uho, nos i grlo na I. katu zgrade s operacijskom dvoranom u istočnom krilu II. kata (1-4).

U ovom povijesnom radu prikazani su neistraženi podatci o mirnodopskim i ratnim kraniocerebralnim i maksilofacijalnim ozljedama bolesnika hospitaliziranih u Zakladnoj bolnici na Rebru tijekom djelovanja bolnice za vrijeme II. svjetskoga rata.

MATERIJALI I METODE

Podatci su dobiveni obradom razvidnih podataka neistraženog arhivalija (prijamni zapisnici, matične knjige) iz bolničke arhive Zakladne bolnice Rebro za vrijeme II. svjetskoga rata, od 1942. do 1945. godine, a istraživanje je odobreno odlukom Etičkoga povjerenstva Kliničkog bolničkog centra Zagreb. Istraživane su mirnodopske i ratne kraniocerebralne i maksilofacijalne ozljede bolesnika zaprimljenih na liječenje u Zakladnu bolnicu Rebro na odjel kirurgije i odjel uha, nosa i grla; njihov broj i podjelu, pripadnost postrojbi/civili, spol, ishod bolesti (izliječeni, poboljšani, neizliječeni, umrli). Nažalost, operacijski protokoli tog vremena nisu dostupni istraživanju, pa nije razvidno koje su kirurški zahvati izvedeni.

REZULTATI

U ispitivanom razdoblju od travnja 1942. do svibnja 1945. godine zbog kraniocerebralnih i maksilofacijalnih ozljeda hospitalizirano je 1532 pacijenata (6,4 %). Muški spol prevladavao je s preko četiri petine ukupnog broja zaprimljenih pacijenata (937; 84 %), a ženski spol značajno manje (178; 16,0 %). Najviše pacijenata bilo je u dobnim skupinama 20-29 godina (334; 30,9 %) te 30-39 godina (269; 24,1 %). Prosječna dob iznosila je 30,19 godina, s najmlađim pacijentom u prvoj godini života i najstarijim s 94 godine.

Najčešće prijamne dijagnoze bile su *Fractura mandibulae* (447; 29,2 %), *Commotio cerebri* (311; 23,3 %) i *Vulnus sclopetarium capitis* (296; 19,3 %), te zajedno sačinjavaju preko dvije trećine ukupnog broja prijamnih dijagnoza (68,8 %). Ostale dijagnoze razvidne su po postotcima zastupljenih u prijmovima u tablici 1. Najviše pacijenata bilo je liječeno u trajanju od sedam dana (353; 31,7 %), no hospitalizacije su nerijetko bile višetjedne, pa i više od deset tjedana, što ukazuje na kompleksnost trajanja liječenja, kirurških zahvata i oporavka. Tako su primjerice, pacijenti s dijagnozom *Fractura maxillae* imali statistički značajno dulje trajanje liječenja od pacijenata s dijagnozom *Commotio cerebri*. Od frakture donje čeljusti koja je bila najčešće evidentirana dijagnoza, najveći broj pacijenata imao je pri otpustu poboljšanje (423), a umrlo je 5; kod frakture nosne kosti i / ili septuma zabilježen je najveći broj poboljšanja (26) bez pomora.

Izliječeno je 7,0 %, poboljšano zdravstveno stanje pri otpustu imalo je 80,6 %, neizliječeno je bilo 2,6 %, a umrlo je 9,1 % hospitaliziranih pacijenata od ozljeda viscero- i neurokranija. Interesantno, najveći broj umrlih zabilježen je zbog dijagnoze *Commotio cerebri* (45 %), potom *Vulnus sclopetarium capitis* (25 %), a slijede *Fractura baseos cranii* i *Fractura cranii* (5,6).

Tablica 1.
Prikaz prijamnih dijagnoza s kraniocerebralnim i maksilofacijalnim ozljedama, učestalošću i postotkom

Dijagnoza	Frekvencija / n	Postotak / %
Fractura mandibulae	447	29,2
Commotio cerebri	311	20,3
Vulnus sclopetarium cranii	296	19,3
Fractura cranii	99	6,5
Fractura baseos cranii	90	5,9
Vulnus lacero contusum capitis	75	4,9
Fractura maxillae	53	3,5
Vulnus sclopetarium faciei	39	2,5
Vulnus laceratum capitis	30	2,0
Contusio capitis	26	1,7
Contusio cerebri	16	1,0
Fractura septi nasi	15	1,0
Fractura nasi	14	0,9
Vulnus explosivum capitis	14	0,9
Haemorrhagia cerebri	7	0,5
Ukupno	1532	100,0

RASPRAVA

Ozljede viscerokranija i neurokranija mogu biti povezane s izravnim ratnim zbivanjima (strijelne i eksplozivne ozljede glave, mozga i lica) ili pak drugim načinima ozljeda (kontuzije, lacerokontuzne rane). Ove ozljede mogu prouzročiti oštećenja viscerokranija, kostolome maksile, mandibule, nosne kosti, kostiju kalvarije ili baze lubanje, oštećenja mozga, intrakranijske hematome raznih sijela. Ekstenzitet ranjavanja zahtijevat će primarne i nerijetko korektivne operacije s posljedičnim visokim postotkom smrti, trajnim invaliditetom i narušnjenjem (7). U ratnokirurškoj literaturi starijega i novijeg datuma ratovanja navodi se 3-13 % kraniocerebralnih ozljeda od ukupnoga broja ratnih ozljeda (7-9).

Kraniocerebralnih ozljeda u ispitivanom materijalu bilo je 964 (62,93 %), maksilofacijalnih 568 (37 %), a ukupni postotak ozljeda glave i lica na zaprimljeni broj u bolnicu bio je 6,4 %. Navedeno ukazuje na veliki broj zaprimljenih bolesnika i ranjenika na razne odjele koje je Zakladna bolnica tada imala, jer je djelovala kao ratna i mirnodopska. Tijekom II. svjetskog rata u Državnoj bolnici u Bjelovaru liječeno je 8 % ratnih kraniocerebralnih ozljeda (10), a Uzelac navodi na našim prostorima učestalost ratnih ozljeda glave u II.

svjetskom ratu 10-12 % s pomorom >30 % (7). U Domovinskom ratu vlastita iskustva ukazala su na 8,4 % ratnih prostrijelnih i eksplozivnih rana glave i mozga u 105. brigadi Hrvatske vojske (8). Smrtnost od 9,1 % u bolničkim uvjetima u ispitivanom materijalu ukazuje da su ranjenici i ozlđeđenici došli u relativno dobrom općem stanju s obzirom da se u Gradu Zagrebu isprva nisu vodile ekstenzivne borbe i da je, kako je navedeno, primarni frontovski pomor od ozljeda glave >30 %. Vjerojatno je tada vrlo učestala dijagnoza *commotio cerebri* zbog koje je značajni broj pacijenata zaprimljen i umro sadržavala i kontuziju mozga s intrakranijskim hematomima raznoga sijela. Kako ne postoje operacijski protokoli i povijesti bolesti nije razvidno koji su bolesnici operirani i zbog čega iz spektra ove dijagnoze. Prosječna dob zaprimljenih pacijenata bila je 30,19 godina, 84 % bilo je muškog spola, što ukazuje na pripadnost vojnim postrojbama mlađih dobnih skupina muškaraca. Brandvold je ukazao u vlastitom materijalu na prosječnu dob ranjenika sa strijelnim ozljedama glave od 21,6 godina (9). Nestrijelne i neeksplozivne ozljede glave i lica, navlastito kostolomi mandibule kao najčešće ozljede i kostolomi maksile kao ozljede s najdugotrajnijim liječenjem i oporavkom ukazuju na možebitne borbene aktivnosti koje nisu izravno povezane s ranjavanjima, već su nastale udarnom silom. No, kako povijesti bolesti nedostaju, to nije moguće statistički znanstveno dokazati, već predmijevati s obzirom na poznate načine ratovanja.

Etablirani kirurzi i otorinolaringolozi, koji su tada radili u Zakladnoj bolnici Rebro u Zagrebu, prema njihovim poznatim biografijama, bili su liječnici s dugogodišnjim iskustvom koji su došli iz bolnica u Vinkovcima, Gline, Bjelovara, Dubrovnika i Osijeka i koji su, prema prijamnim dijagnozama i njihovim poznatim spektrom operacijskog programa, obavljali sve kirurške zahvate iz ondašnje ratne i mirnodopske neurokirurgije i kirurgije glave i vrata. Za sada ne postoje izvorni radovi koji su obrađivali sličnu problematiku u drugim zagrebačkim bolnicama kako bi se mogli objediniti i dobiti realnu sliku zbivanja oko zbrinjavanja kraniocerebralnih i maksilofacijalnih ozljeda, pa je ovaj prikaz za sada prilog medikohistoriografiji II. svjetskoga rata u jednoj zagrebačkoj bolnici kao izravni primjer ratne medicine.

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SUMMARY

CRANIOCEREBRAL AND MAXILLOFACIAL INJURIES TREATED IN HOSPITAL REBRO IN ZAGREB DURING 1942.-1945.

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This paper presents unexplored data on peacetime and wartime craniocerebral and maxillofacial injuries hospitalized at the Foundation Hospital Rebro in Zagreb 1942-1945. 1532 patients were hospitalized, of which 964 (62.93%) had craniocerebral injuries and 568 (37%) maxillofacial injuries. The average age of the admitted patients was 30.19 years, male of 84%, indicating affiliation to military units of younger age groups of men. The most common admission diagnoses were *fractura mandibulae* (29.2%), *commotio cerebri* (23.3%) and *vulnus sclopetarium capitis* (19.3%). 7.0% of those admitted were cured, 80.6% had an improved health condition at discharge, 2.6% were untreated, and 9.1% of hospitalized patients died. The highest number of deaths was recorded due to the diagnosis of *commotio cerebri* (45%), followed by *vulnus sclopetarium capitis* (25%), followed by *fractura baseos cranii* and *fractura cranii.*

Key words: craniocerebral injuries, maxillofacial injuries, II. World War, Croatia, Hospital Rebro, Zagreb

PRIČICE O OSOBAMA S MORBUS ALZHEIMER

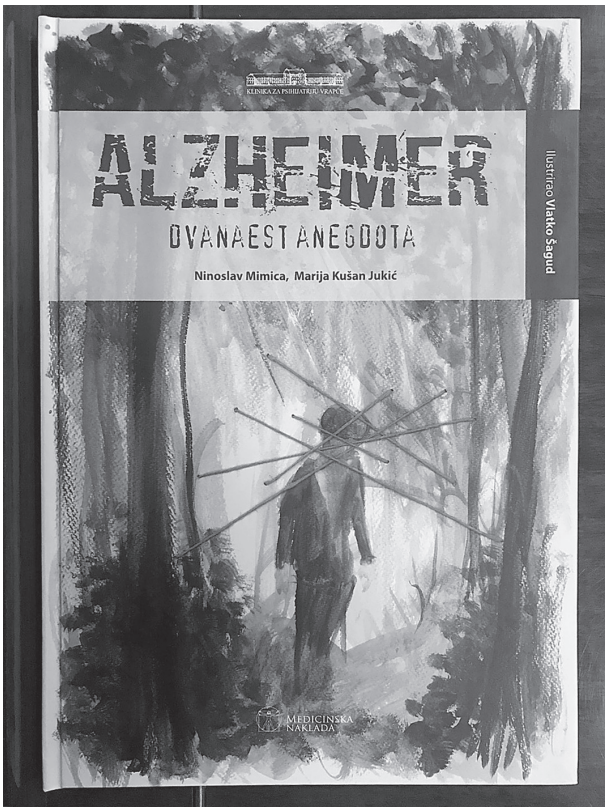
N. Mimica, M. Kušan Jukić (ur.)
Zagreb: Medicinska naklada i Klinika za psihijatriju Vrapče, 2018.

Sakupljenih dvanaest anegdota, popraćenih ilustracijama iz života pacijenata oboljelih od najpoznatije demencije – Alzheimer, rječito govore slikama i pričama o suštini kliničkog fenomena, naravi i dogodovštinama ovog nozološkog entiteta, koji može (a valjda neće!) pogoditi bilo koga od nas. Na limesu s humorom (da nije tragično bilo bi komično) ove prič(ic)e prezentiraju svu nesuvislost u izričajima i ponašanju pacijenata te *nolens – volens* nagnaju ponekad čitatelja i na smijeh (u tome im je i svrha, zlo ne bilo), kao na fiziološku reakciju humora prezentiranog bez zloduhe namjere, već da (nas) i zabavi i opomene. (Ali za prevenciju je često već prekasno, a možda je ne može ni biti). Etiologija leži u genima, malo i u rizicima koje život sa sobom neminovno nosi (oštećenja etilnim alkoholom, nikotinom, distresima, frustracijama, teškim psihofizičkim životnim nevoljama, etc. – mnogo toga još nepoznatog).

Mladi akademski kipar – ilustrator Vlatko Šagud svaku je anegdotu prikazao i crtežom u boji, kako i priliči svakoj depresivno intoniranoj, zamalo tragičnoj tematici. Lijepo opremljenoj knjizi u tvrdom povezu, otisnutoj na *kunstdruku* zahvaljujemo Medicinskoj nakladi i njenoj entuzijastičnoj vlasnici i pregalačkoj urednici gospođi profesor Anđi Raič, a isto tako i nadasve aktivnom i angažiranom uredniku ove knjige (i mnogih drugih!) prof. dr. sc. Ninoslavu Mimici te koautorici dr. sc. Mariji Kušan Jukić.

Suizdavač je svakako i Klinika za psihijatriju Vrapče, opet uz riječ nakladnika prof. prim. dr. sc. Vlade Jukića. Već znamenita izdavačka kuća Medicinska naklada vrelo je skoro tisuću knjiga, mahom udžbenika za medicinske fakultete i srednje škole u Hrvatskoj i šire, ali i knjiga poezije liječnika pjesnika u biblioteci Knjigolijek.

Knjiga *Alzheimer – dvanaest anegdota* poslužit će svim svojim čitateljima, rođacima, ukućanima, njegovateljima, medicinskim sestrama i tehničarima, svima onima koji imaju u obitelji takvog teškog, napornog bolesnika, teško shvatljivog zbog kognicijskog i memorijskog deficita, kao i svim ostalima koji dolaze u kontakt i na bilo koji način komuniciraju s njima (pa



i čistačicama, domarima mirovinskih domova i dr.). Tako se i ostali ljudi mogu neposredno, humorom, upoznati s pojavnošću ove bolesti, životom njenih žrtava, svakodnevnim ispadima pacijentovih zbivanja iz njihovog, ne u biti za njih nesretnog života, ali lišenog dimenzije socijalnih kvaliteta, „životinjajući" kao biljke, vegetirajući na rubu egzistencijskog punovrijednog vegetativnog življenja, zadovoljavajući osnovne vitalne potrebe (fiziološke, prehrambene, somnološke, motoričke…). Poremećajni ispadi u spoznajnim, glede pamćenja i sjećanja, pozornostnim i drugim (ne uvijek i porivnim, koje sistiraju na kraju!) ego-funkcijama u ovih bolesnika, ekstrahiranim direktno iz svakodnevnog života od danas do sutra, dovoljno oslikavaju kapacitete njihovih centralno-nervno-sustavnih mogućnosti. Tu se radi o fugama, zaboravljanju pogotovo neposrednih zbivanja prema arteriosklerotskom tipu, neprepoznavanju bližnjih iz svakodnevne okoline, nemogućnošću satisfakcije banalnih navika i običaja

(oblačenje, npr. bračni cjeloživotni partner kao prvi puta viđen, etc.), dezorijentacija na auto-alo-spacio-temporalnim planovima. Mnoštvo priča, također na bazi istinskih događaja, govore o stavovima i projekcijama i projektivnim identifikacijama nas još uvjetno rečeno zdravih prema onima koji su nažalost već izgubili te funkcije „zahvaljujući" deterioriranju devastirajućeg dementnog, ne nužno senescencijskog procesa ireverzibilnog, sve do nužno letalnog egzitusa.

Nije to zbirka izmišljenih, prepričanih viceva, ekscesa o bolesnicima ove infaustne finalne, terminalne bolesti, ozbiljnog inveteriranog patološkog demencijskog procesa i stanja. Mb. Alzheimer (pogrešno pisanog kao AB - (abortus) Alzheimerova bolest u doktorskom žargonu (slengu).

To su nažalost vrlo autentične, istinite, vjerodostojne priče iz njihovog življenja. Da nije žalosno - bilo bi veselo, a možda i jeste, zna se i zašto. Nama, kojima još ne popušta memorijska funkcija i drugi oblici zdravlja. Tako i mi ne možemo uživjeti se, simbiotski empatijsko-simpatijski (ne znamo što nas još čeka), ne možemo nekad odoljeti da se barem ne nasmiješimo kad neka (ili svaka) od tih priča ne zapne nam za oko kad ju pročitamo. Apsurd je logika snova kažu surrealisti, ali ovo nisu sanjane šale.

Može se iz neposrednog doživljaja u radu, njegovanju i bavljenju životom ovih ljudi zlatnog doba ove omaške, pošalice dogoditi da nas opomenu da možda tako nešto i nas jednom čeka. Ali mi još koristimo mehanizme obrane Anne Freud, među koje neki ubrajaju i humor. Tu značajnu ulogu ima projekcija. Naime, naše strahove, mane, pogreške rado vidimo kod drugih, projiciramo u njih kao u žrtvenu janjad (jarce). Bolje da se to dogodi drugima nego (još, već) nama. "Neka visi Pedro" - kažu u jednom vesternu. Neka onaj Drugi u našoj mašti ispašta zasad naše eventualne (buduće) grijehe (ili prošle). Da ne bi nas, nedajbože, zakačilo još i to. Neki radije umru (od *Herzschloga* ili *Hirhschloga*), pa to ne stignu doživjeti (kao od karcinoma prostate, koji sporo raste pa se u SAD ni ne operira, jer je zahvat skup, a kapaciteti mali).

Ova knjiga već pomaže medicinskim djelatnicima i bližnjima u razumijevanju njihovih pacijenata. Općenito također služi i u propagiranju destigmatizacije, jer bolesnici i dementni ljudi se označavaju, markiraju, etiketiraju, izlažu kao manje vrijedni, dizabilitetni, invalidni («nezdravi» - *valetudo* - zdravlje). Ispravno, to su ljudi s posebnim potrebama – da se drugi (i društvo, država) za njih pobrinu, skrbe, pomognu im, da humano prežive ono malo što im je preostalo, jer eutanazija je neetična i nelegalna. A svaki im je dan od Boga – prirode (*Deus sive natura*), poklonjen. A zadužili su nas investirajući emocionalno i materijalno u nas dok smo mi bili potrebiti njihove skrbi. Osvještavanje mogućeg tako života i senescencijskog nametnutog procesa dobra je priprema za eventualno predstojeće. Da bismo na vrijeme razumjeli neka očekivanja i - bili humani. Kasno je na Svisvete paliti svijeće i nositi cvijeće, moliti…

Priče su to u ovoj knjizi saturirane osjećajnošću, praćene afektom, pa i samožrtvovanjem, mogu biti intonirane salezijanskom dušobrižnošću samarićanskim čovjekoljubljem, sažaljenjem prema onima koji pate, pomaganjem u nevolji.

Rad s bolesnicima od Mb. Alzheimer svjestan je *memento morbi*, ali i *memento mori*, jer su oni bliže svojoj nekropoli, kraju svog življenja, pristupu *Thanatosu*, veslaču – lađaru Haronu i anđelima koji se vide onkraj svijesti – transcendentalno – zapravo kroče u nesvijet - nesvjest ništavila. Iz te se vidljive perspektive motri život, svijet i bitak sasvim drugačije – pred iskorakom u *status nihil*.

LJUBOMIR RADOVANČEVIĆ

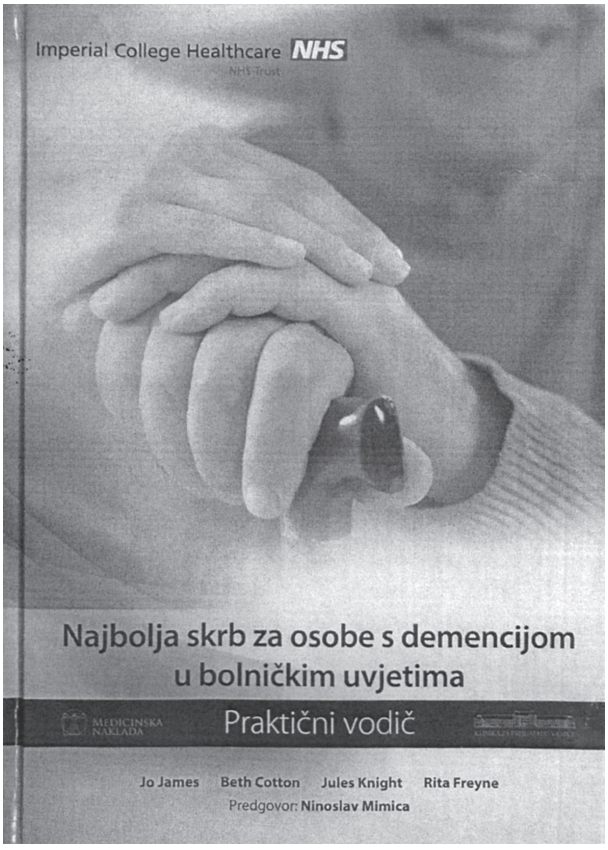
KAKO POMOĆI OSOBAMA S MB. ALZHEIMER (NAJBOLJA SKRB ZA OSOBE S DEMENCIJOM U BOLNIČKIM UVJETIMA)

Jo James, Beth Cotton, Jules Knight, Rita Freyne
(prijevod s engleskog M. Gros)
Zagreb: Medicinska naklada i Klinika za psihijatriju Vrapče, 2018.

Praktični priručnik i vodič autora Jo James, Beth Cotton, Jules Knight i Rita Freyne «Najbolja skrb za osobe s demencijom u bolničkim uvjetima» bit će (i već jest), veoma koristan svim djelatnicima, rođacima, ukućanima, njegovateljima koji dolaze u kontakt, distribuiraju skrb, brigu, ljubav, obraćaju pažnju bolesnicima od Alzheimerove bolesti. Ovaj kompedij koji na kraći način izlaže primjenu prilagođenu prvim potrebama onima koji uče kako pomoći onima koji trpe demenciju. Knjiga je rađena vrlo sistematski, pruža mnoštvo informacija kako pristupiti bolesniku s raznih njegovateljskih aspekata. Neophodna je svim bližnim ljudima koje zanimaju kontakti – verbalni i neverbalni, a ovim dementnim pacijentima, koji posao, a i sama komunikacija mogu biti vrlo kompliciрani, jer su bolesnici duhovno odsutni, otežano se snalaze, pamte, a sve to zahtijeva veliki stupanj pažnje i tolerancije. Dezorijentirani prema sebi, drugima, u mjestu, prostoru i vremenu, inklinativni bjegovima – fugama, te se mora na njih, kao i na djecu prije pete godine života stalno motriti, obraćati pozornost da se ne bi u trenu nekamo izgubili. Kvaliteta življenja im je sa socijalnog gledišta vrlo oskudna, ne razumiju relacije s drugima, manifestiraju ispade u kogniciji, memoriji, pozornosti i ostalim ego-funkcijama, te to rezultira potrebom za konstantnom paskom. Neki od bolesnika od Alzheimerove demencije zapravo vegetiraju, od danas do sutra, jer nemaju više životne perspektive….

Priručnik je s engleskog preveo dr. sc. Mario Gros, dr. med., radiolog osječke Kliničke bolnice Sveučilišta Josip Juraj Strossmayer. To je učinio za privatne potrebe svoje sestre, gospođe Jadranke Vuković iz Subotice, osnivačice udruge „Betanija Alchajmer".

Zahvaljujući voditelju Referentnog centra Ministarstva zdravstva Republike Hrvatske za Alzheimerovu



bolest i psihijatriju starije životne dobi, pročelniku za biologijsku psihijatriju i psihogerijatriju Klinike za psihijatriju Vrapče, Medicinskog fakulteta Sveučilišta u Zagrebu, predsjedniku Hrvatskog društva za Alzheimerovu bolest i psihijatriju starije životne dobi, HLZ i predsjedniku Hrvatske udruge za Alzheimerovu bolest – prof. dr. sc. Ninoslavu Mimici ova je vrijedna knjiga ugledala dana u izdanju Medicinske naklade i Klinike za psihijatriju Vrapče u Zagrebu.

LJUBOMIR RADOVANČEVIĆ

Prof. Dr. Ranko Mladina
umirovljeni ORL specijalist
Klinika za uho,grlo i nos i kirurgiju glave i vrata
KBC Zagreb

Poštovani gospodine glavni uredniče,

Želio bih čestitati gospođi profesorici Bašić – Jukić, uvaženoj internistici KBC Zagreb, na trudu uloženome u pisanje vrlo vrijednog rada koji je objavljen u najnovijem broju časopisa Acta Medica Croatica. Rinosinusološki me dio njena članka nadahnuo i potakao na pisanje gornjih redaka i hvala joj za to! U tom pogledu, dometnuo bih tek da u hrvatskom jeziku rinosinusolozi upalu sinusa pišu kao **sinuitis**, a ne sinusitis. To je zato jer je na latinskom jeziku nominativ imenice sinus upravo takav, dakle **sinus**, ali genitiv ove imenice je **sinu**. Upalu nekog organa označava se latinski da se genitivu dotičnog organa doda nastavkak-**itis**, pa je, prema tome, pravilan izraz za upalu sinusa **sinuitis**, a nikako **sinusitis.** U anglosaksonskoj je literaturi uobičajeno pisati **sinusitis**, ali to je posljedica tamošnje niske razine školovanosti u pogledu stranih, a poglavito latinskoga jezika. „Sinusitis" je jednostavno opće prihvaćen idiom u pisaca na engleskom i drugim zapadnoeuropskim zemljama, i nije na nama da to ispravljamo.Nadalje,bez obzira na to, nikako ne bi trebalo zaboraviti da je arhaični, ali izvorni latinski naziv za ovaj sinus **antrummaxillaris.** Odatle je naziv za kirurško formiranje otvora u području medijalne stjenke maksilarnoga sinusa: **antrostoma**, nipošto anterostoma. Nadalje, u četvrtoj je rečenici sažetka rada navedeno da je „ obradom pronađena destrukcija tkiva oko zahvaćenog paranazalnog sinusa", ali podatci o vrsti navedene destrukcije u kasnijem tekstu nedostaju. Pri kraju sažetka je navedeno, kao zaključak, da je u opisanim slučajevima preporučljiv „agresivan kirurški pristup s odstranjivanjem nekrotičnog tkiva", ali kasnije, u samome tekstu, nema detaljnijih opisa kako se to „agresivno" operira sinus.Ja znam kako se to radi jer je do 1990. godine to bio i moj kirurški djelokrug. Uvođenjem endoskopske sinusne kirurgije (prvu sam takvu operaciju u nas napravio, nakon edukacije u Austriji, Njemačkoj i SAD, dana 7. prosinca 1990. u lokalnoj anesteziji), „agresivno" je operiranje sinusa u načelu otišlo u povijest, osim, naravno, u slučajevima malignih bolesti. Nadalje, gledano rinosinusološki, u tekstu se pojavljuju dvije slike, obje su CT snimke sinusa, ali, nažalost, samo u aksijalnim projekcijama (grubo rečeno-vodoravnim), a za detaljnu spoznaju o stvarnom stanju sinusa potrebna je svakako i tzv. koronalna projekcija (grubo rečeno-vertikalna). Tako se u opisu slike 1u navedenom članku navodi kako se vidi posve ispunjen desni maksilarni sinus, ali to se ne može tvrditi ako nema i koronalne projekcije. Jer, može se raditi o promjenama samo na dnu ili najviše u donjoj polovini sinusa, ali kakvo je stanje cijele šupljine iz ove slike se ne zna. Navedena slika 1 je učinjena u razini sloja koji je na slici u istoj razini s donjim nosnim hodnikom, dapače, lijepo su prikazani stražnji dijelovi nosne pregrade i oba stražnja pola donjih nosnih školjki, epifarinks pa čak i oba ušća Eustachijeve tube. Uz sav moj trud, na ovoj slici ne vidim nikakvih znakova okolne destrukcije dotičnog maksilarnog sinusa. Usput, na nosnoj se pregradi jasno vidi ono što se na aksijalnim projekcijama posebno lako prepozna, a to je deformacija lamine perpendikularis (jedan od koštanih dijelova septalne plohe, ujedno i najveći dio septuma) i to u obliku slova „C", što u rinologiji, kako u nas tako i u svijetu, već više od tri desetljeća označavamo kao gore spomenutu deformaciju septuma tipa 3. Nadalje, na slici 1 se jasno vidi da nedostaje prednji dio nosne pregrade, tj. onaj hrskavični dio (lamina kvadrangularis). Defekt u ovome dijelu septuma ne možete ni po kojim kriterijima dovesti u vezu s Aspergillusom nađenim u čeljusnim sinusima (1,2). Najvjerojatnije se ovdje radilo o kroničnom nosnom vestibulitisu (iz anamneze se doznaje da je bolesnik godinama muku mučio s krustama u nosu), a nosni vestibulitis nije ništa drugo do li upala kože koja prekriva nosno predvorje. Bilo bi dobro znati je li bolesnik imao u anamnezi imao smetnje tipa učestalih, povremenih krvarenja iz nosa, poglavito iz uvijek iste strane, varicescruris, hemoroidalni sindrom i je li imao (ili netko od bliskih srodnika) vaskularni cerebralni inzult . Ova su patološka stanja vrlo često povezana s rekurirajućim krvarenjima iz nosa potaknutih upalom kože nosnoga prevorja, a na terenu proširenih vena u tzv. Kieselbachovu pleksusu smještenom na septumu u samom predvorju (sindrom poznat pod nazivom RecurrentEpistaxisfromKiesselbach'sAreaSyndrome ili skraćeno REKAS) (3-7). Česta krvarenja i intervencije liječnika (tamponade, kauterizacija krvareće, ektatične žilice) mogu rezultirati konačnim prpadanjemseptalna tkiva i na CT snimkama se može vidjeti da nedostaje septum u posve prednjim dijelovima. Daleko je najčešći uzrok vestibulitisunasi, pa i REKAS-u, bakte-

rija Staphylococcuspyogenesaureus, a nikako gljivica Aspergillus. Dakle, najvjerojatnije se ipak radilo se o dva odvojena klinička entiteta. Nadalje, na slici 2 se opisuje stanje nakon liječenja, ali, ako već uspoređujemo dvije CT snimke istoga sinusa u aksijalnim projekcijama (ili bilo kojim drugim) onda neka budu snimke iste razine. Razina snimke na slici 2 je razina srednjeg nosnog hodnika ili čak nešto kranijalnije jer se vide glave gornjih nosnih školjki i praktički čitav sfenoidalni sinus! To u sinusologiji nikako nije usporedljivo (donji i srednji nosni hodnik). Nadalje, iz ove je slike posve jasno da je netko korektno napravio zahvat na desnom čeljusnom sinusu i to je, prema mome znanju, napravio tzv. srednju **antrostomu** Ovaj je zahvat zacijelo napravljen, ako je to rađeno na Rebru, od strane rebarskog otorinolaringologa, endoskopski. A endoskopska kirurgija ne spada u „agresivne" kirurške zahvate. Obrnuto! Vrlo je precizna i djelotvorna, ali ne i agresivna.

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Dragi Uredniče,

Veselimo se interesu koji je prikaz slučaja „Aspergiloza paranazalnih sinusa u bolesnika s transplantiranim bubregom" pobudio u čitatelja Vašeg časopisa i zahvaljujemo na mogućnosti da odgovorimo na pismo prof. Mladine.

Aspergiloza paranazalnih sinusa je rijetka komplikacija u bolesnika s transplantiranim bubregom koji su zbog primjene imunosupresiva izloženi različitim patogenima. U prikazu slučaja smo iznijeli internistički pogled na problem, te ovim putem zahvaljujemo prof. Mladini na iscrpnom pregledu problema sa strane otorinolaringologa.

S poštovanjem
Prof. dr. sc. Nikolina Bašić-Jukić

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Manuscripts and all attachments are submitted in Croatian or English language in e-form (Word for Windows), font Times New Roman, font size 11, not more than 15 pages, 1.5 line spacing, with 2.5 cm left, right, top and bottom margins. The number of figures and/or tables is limited to 10 and the list of references to 50. The manuscript should be divided into the following sections: title page, summary in Croatian and English language, organizational sections depending on the type of manuscript, attachments (figures and tables), and list of references. If the paper is written in Croatian language, the extended structured summary (containing title of manuscript, author names, affiliation name and address, objective, methods, results, discussion and conclusion) of not more than 600 words should be written in English language, and *vice versa*. Title page: full title of the manuscript, first and last names of all authors (no degrees), names of all authors' affiliations, and up to 6 key words for fast identification and classification of the paper. Original research articles: introduction, aim, methods, results, discussion, conclusion and references. The introduction section briefly presents the problem of the study; the aim section gives short description of the study purpose. Methods should be so presented to enable reproducibility of the research described; widely known methods are not described but referred to by respective reference number. Generic names of drugs should be used (trade names can be written in parentheses with first letter capitalized). Results should be presented clearly and logically, and their significance demonstrated by appropriate statistical methods. In discussion section, the results obtained are presented and compared with current state-of-the-art in the field. Conclusions should be so structured to correspond to the study objective set above. The list of references should begin on a separate page and numbered in the order of their first citation in the text. References are cited according to the Vancouver style, with journal abbreviations as stated in Index Medicus. The list of tables with their numbers, titles and possible legend below tables, and the list of figures with their numbers, captions and possible legend below figures should be written on a separate page. Tables should be numbered consecutively and entitled; tables are written each on a separate page and in PDF format. Figures should be numbered consecutively and marked with the first author's name; figures are presented in JEPG or TIF format, resolution no less than 300 dpi.

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