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Original article

The impact of TP53 and PTEN tumor suppressor genes on response to different breast cancer treatment modalities

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Summary

Introduction. Breast cancer (BC) is the most frequent type of malignancy and the leading cause of cancer related death among women worldwide. BC is exceptionally heterogeneous disease and therefore distinct treatment modalities are necessary to address these differences. The aim of our study was to investigate the impact of TP53 and PTEN tumor suppressor genes (TSGs) inactivation on BC response to different treatment modalities and their possible cooperation, on post-operative BC samples.

Methods. Patients were classified, based on applied adjuvant therapy, into four distinct groups: those that received hormonal therapy (HT) only, hormonal therapy combined with chemotherapy (HT/CHT), hormonal therapy combined with chemo and biological therapy (HT/CHT/H), and other systemic therapies that exclude HT. Functional inactivation of TP53 and PTEN TSG's were studied by mutation, loss of heterozygosity (LOH) and hypermethylation analysis.

Results. Our results revealed that TP53 gene was altered in 63 out of 90 specimens (70%), while the frequency of PTEN alterations was slightly lower, 54 out of 90 (60%). Simultaneous inactivation was detected in 43 tested samples (48%) with significant association between two analyzed TSGs. Further, we found that TP53 status has significant influence on patients' therapy response. Contrary to this, no significance was found between mutational status of PTEN and various treatment modalities. However, significant association was found between the type of applied therapy and simultaneous alterations of these two TSGs (p = 0.00001).

Conclusion. Patients with wtTP53 show significantly better therapy response regardless of the type of therapy, compared to carriers of altered TPp53 gene.

Keywords: breast cancer, p53, PTEN, adjuvant therapy

Introduction

Breast cancer (BC) is the most frequent type of malignancy and the leading cause of cancer related death among women worldwide [1]. More than 70% of all diagnosed invasive BCs express steroid receptors and, as such, are subjected to endocrine therapy [2]. Steroid receptor positive BC is not a single disease, rather, it encompasses several entities with significant differences in clinical course [2]. Distinct treatment modalities are necessary to address these differences especially since BCs often develop endocrine therapy resistance. Therefore, endocrine therapy is often combined with other types of systemic adjuvant therapies - chemotherapy and/or targeted biological therapy (trastuzumab and more recently mTOR and cyclin-dependent kinase 4/6 inhibitors) [3-5]. Whether the management of endocrine responsive BCs will use combined treatment strategies or not, depends on clinical, pathohistological and molecular characteristics of the tumor including lymph node invasion, tumor size, human epidermal growth factor receptor 2 (HER2) status, molecular subtype etc. Numerous factors and their interplay determine BC response to therapy and clinical outcome.

Tumor suppressor genes have a vital role in inhibiting neoplastic transformation. Among so far studied, TP53 (p53) and phosphatase and tensin homologue (PTEN) are the most frequently altered in human cancers [6, 7]. TP53 and PTEN inactivation may occur either through mutation, allelic losses, promoter hypermethylation, non-coding RNA-associated gene silencing, protein sequestration or due to alterations of the genes involved in their regulation [8–11]. p53 is activated in response to cellular stress and has a central role in an immensely complex anti-proliferative network that incorporates numerous biological processes including apoptosis, senescence, cell cycle regulation, differentiation, DNA repair, metabolism, angiogenesis and immune response [7, 12]. Mutations are a frequent mechanism of TP53 inactivation and are identified in about 30% of steroid receptor positive BCs [13]. TP53 mutations not only abrogate p53 protein's tumor suppressor role but may give rise to new (gain-of-function) capabilities that promote tumorigenesis and progression of BC [11]. Mutations in one TP53 allele are commonly accompanied by the loss of the wtTP53 allele (loss of heterozygosity (LOH)) [14]. It seems that during tumor progression, there is a strong selective pressure for TP53 LOH [14]. According to Silwal-Pandit et. al, TP53 LOH was detected in 81% of BCs with one mutated allele, and in up to 52% of steroid receptor positive BCs with wtTP53 [15]. Estrogen receptor alpha (ER α) is highly expressed in steroid receptor positive BC and associated with tumor initiation and growth. ER α and p53 engage in a complex interplay of mutual regulation [16]. There is a positive feedback loop between ER α and p53 – they enhance each other's transcription [16]. Moreover, ER α can regulate p53 on post-transcriptional level and directly interact with p53 to modulate its function [16]. ER α stabilizes p53 by blocking MDM2 inhibition of p53, but, on the other hand, prevents p53 induced apoptosis, blocs the transactivation of the p21 promoter etc. [16]. ER α clearly has a dual role in regards to p53. The fate of BC may depend on the fine balance between ER α and p53.

Phosphoinositide-3 kinase (PI3K) / AKT-/ mammalian target of rapamycin (mTOR) signaling pathway is a crucial mechanism that stimulates cellular survival, growth, proliferation and migration [17]. Activation of PI3K/ AKT/mTOR pathway has been associated with initiation and progression of numerous malignancies including BC [18]. PI3K is frequently hyperactivated in steroid receptor positive BC due to PIK3CA mutations [19]. The main 'brake' is the tumor suppressor PTEN which negatively regulates the pathway and attenuates PI3K activation [17]. LOH is the most common mechanism by which PTEN function is lost in steroid receptor positive BC [20]. Unsurprisingly, PTEN loss was associated with poor outcome and resistance to endocrine and chemotherapy in BC [20,21]. There is ample evidence of PTEN/p53 interaction and complex crosstalk [22]. p53 was shown to stimulate PTEN transcription and PTEN to enhance p53 stability [22]. The loss of PTEN and TP53 may have a synergic effect in tumor promotion [22].

In the present study, we aimed to investigate the impact of TP53 and PTEN inactivation on the BC response to different treatment modalities as well as their possible cooperation.

Methods

This study was performed on 90 invasive breast cancer (BC) and corresponding normal tissue samples collected after surgery, from the Institute of Oncology and Radiology of Serbia, in a period between 1988 and 2013. The age of patients ranged from 29 to 78 year's. Diagnoses of BC's and hormonal status, histological grade and regional lymph node involvement have been determined after hematoxylin-eosin staining. The most of analyzed samples were steroid receptor-positive (94.5%) and classified as invasive ductal, 53 out of 90 (58.9%) or invasive lobular, 37 out of 90 breast carcinomas (41.1%). All relevant clinical and patohistological parameters

Parameters		Values
Age at onset, years (mean)		29 – 78 (59)
Follow-up, months (mean)		11 – 228 (80)
Number of patients (%)		90 (100%)
Tomo of Broad Consistents	Invasive Ductal (IDC)	53 (58.9%)
Type of Breast Carcinoma	Invasive Lobular (ILC)	37 (41.1%)
	Grade 1	5 (5.6%)
Histological grade	Grade 2	74 (82.2%)
	Grade 3	11 (12.2%)
	ER+/PR+	68 (75.6%)
Steroid receptor status	ER+/PR-	17 (18.9%)
-	ER-/PR-	5 (5.5%)
	Negative (N0)	24 (26.7%)
I	Positive (N1)	51 (56.7%)
Lymph hode status	Positive (N2)	10 (11.1%)
	Positive (N3)	5 (5.5%)
Distant materias	Present	30 (33.3%)
Distant metastases	Absent	60 (66.7%)
	HT only	56 (62.2%)
Type of therapy	HT/CHT	23 (25.6%)
	HT/CHT/H	4 (4.4%)
	Other Th	7 (7.8%)
Severity of malignancy	Mild	41 (45.6%)
	Severe	49 (54.4%)

Table 1. Clinical and histopathological characteristics of samples

ER - Estrogene receptor; *PR* - Progesterone receptor; *HT* - hormonal therapy; *HT/CHT* - hormonal therapy combined with chemotherapy; *HT/CHT/H* - hormonal therapy combined with chemo and biological therapy; Other *Th* - other systemic therapies that exclude hormonal therapy

(age, tumor type, pTNM stage, steroid receptor status, type of therapy, histological grade) were retrieved from patient's medical records and summarized in table 1.

The patients were classified, based on applied adjuvant therapy, into four distinct groups: those that received hormonal therapy (HT) only, hormonal therapy combined with chemotherapy (HT/CHT), hormonal therapy combined with chemo and biological therapy (HT/CHT/H), and other systemic therapies that exclude HT, for example CHT or H.

Functional inactivation of TP53 and PTEN TSG's by mutations, loss of heterozygosity (LOH) and hypermethylation have been determined on genomic DNA extracted from paired samples of tumor and adjacent normal tissue.

Genomic DNA was extracted using phenol/chloroform/isoamylalcohol precipitation protocol [23]. The quality, concentration and purity of genomic DNA was verified by electrophoresis and spectrophotometry (Nano-Drop Technologies, Wilmington, DE, USA). Isolated and purified DNA was stored at +40C until further analyzes.

Loss of heterozygosity (LOH analyses), was performed by fragment analysis with two sets of highly polymorphic microsatellite markers chosen to cover loci where TP53 and PTEN genes mapped at 17p13 and 10q23, respectively. Microsatellite markers used in this study were selected according to the official criteria of heterozygosity, i.e. heterozygosity greater than 0.7 in different human populations. The choice of microsatellite markers and locus-specific PCR conditions were taken from published sources [24–25]. Forward primers for both sets of selected markers were 5'-labeled with fluorescent dyes.

The set for LOH analyzes of TP53 included following markers: Fam labeled TP53 pentanucleotide, PET labeled TP53 dinucleotide, Ned labeled D17S1537 and D17S786 labeled with Vic. Another set of five polymorphic microsatellite markers selected to cover deletions at the whole PTEN locus included: D10S579, D10S1765, D10S215, and D10S541, labeled with Fam and AFM086wg9 which was labeled with PET dye.

Locus specific amplicons, mixed with HiDi formammide and GeneScan-500 LIZ Size Standard, were separated by capillary array electrophoresis on an ABI Prizm 3130 automated sequencer (Applied Biosystems). Subsequently, collected data were analyzed with GenneMapper software (Applied Biosystems). Each analyzed tumor specimen had its own reference, i.e. DNA isolated from normal breast tissue of the same patient was used as a control. The DNA from normal breast tissue adjacent to tumors of the same patient was used as reference, ie each analyzed tumor sample had its own control.

The occurrence of only one peak in the reference, referred that selected marker was uninformative (homozygous). Opposite, a marker was considered informative when two allelic peaks were identified in a control specimen (heterozygous). To determine allelic imbalance we compered (for all informative cases) peak high ratios of microsatellite allels between normal and tumor tissue of the same patient and calculated it automatically by GeneMapper software using the following formula: (peak height of normal allele 2)/ (peak height of normal allele 1) divided by (peak height of tumor allele 2)/(peak height of tumor allele 1). This procedure has been done for all informative cases. A sample was defined as an LOH candidate for particular locus if the ratio values were less than 0.66 and higher than 1.5. When the ratio values were less than 0.66 and higher than 1.5, a sample was considered to be an LOH candidate for particular locus.

Frequently mutated exons of the TP53 gene (5–9) were amplified by PCR and screened for mutations using PCR–single-stranded conformational polymorphism (PCR-SSCP) analysis, according to Orita et al [26]. Amplimers and PCR conditions were described in Sakai et al [27]. In order to avoid false positive and/ or false negative results, all samples were ex-

amined for the presence of mutations from at least 3 independent PCR amplifications and under at least two different experimental SSCP conditions [28–29]. The DNA isolated from the blood of healthy individuals was used as a negative control.

In order to confirm the results obtained by PCR-SSCP, mutated samples were subjected to sequencing. Sequences were determined with Applied Biosystems Incorporated dye terminator sequencing kit according to the manufacturer's instructions on an ABI Prism 3130 automated sequencer (Applied Biosystems, Foster City, Calif).

The methylation status of PTEN tumor suppressor gene was determined by methylation-specific PCR (MSP). The genomic DNA extracted from breast tumor tissues were modified by sodium bisulfite treatment according to procedure described by Herman et al [30]. In this study, two different sets of primers (set I and set III) were used for MSP reactions [31]. Both set of primers were created to avoid PTEN pseudogene amplification. Commercially available, Unmethylated and CpG Methylated Human Male genomic DNA (Thermo ScientificTM) served as positive control.

The comparison of TP53 and/or PTEN functional inactivation (by mutations, LOH and/or hypermethilation), type of subjected therapy and relevant patohistological parameters, with each other and with the survival (disease free survival, overall survival and breast cancer specific survival) were performed by univariate and multivariate analysis using the Cox proportional hazards model and the Kaplan-Meier test. The level of significance was set at 0.05.

Results

This study included 90 women with breast cancer, classified as invasive ductal (53/90) and invasive lobular (37/90) breast carcinomas. Clinical and histopathological characteristics of examined breast cancer specimens are summarized in table 1. Study included seventy-nine postmenopausal and eleven premenopausal women, most of whom were steroid receptor (ER and/or PR) positive (94.5%). The age at disease onset ranged from 29 to 78 years (mean 59), while the mean overall survival was 80 months (11–228 months). The specimens were further stratified into mild or severe group depending on disease severity. Histological grade, TNM status and tumor type were used as criteria for this distribution. Patients were subjected to different systemic adjuvant therapy depending on steroid receptor status and histopathological and clinical criteria:

- hormonal therapy only (HT)
- hormonal therapy combined with chemotherapy (HT/CHT)
- hormonal therapy combined with chemo and biological therapy (HT/CHT/H)
- other systemic therapies that exclude HT, for example CHT or H only.

Tamoxifen (TAM) was the drug of choice among hormonally treated patients in almost all cases. Namely, only one patient out of fifty-six received anastazol - aromatase inhibitor, while all the others were tamoxifen treated. On the other side, patients from the second therapy group whose treatment was based on chemotherapy (HT/CHT), received CMF (Cyclophosphamide Methotrexate Fluorouracil), FAC (5-Fluorouracil, Doxorubicin, Cyclophosphamide), Taxotere, EC (Epirubicin and Cyclophosphamide) or any combination of listed drugs in addition to TAM.

To evaluate efficiency of different treatment regimens on the overall survival, Kaplan-Meier survival curves were generated. According to obtained results, survival of patients who underwent hormonal therapy only, was significantly longer (Figure 1) then the survival of those treated with other therapy combinations. The greatest statistical significance in overall survival was detected between HT and HT/CHT therapy groups (Figure 1). Further analyses (Cox regression) confirmed obtained results, suggesting that patients receiving hormone therapy had at least 3 times greater survival rates compared to patients on other therapies (Table 2).



Figure 1. Kaplan-Meier survival curves for different treatment regimens

Women treated with hormonal therapy only (HT), lived significantly longer compared to other three therapy groups: HT/CHT - hormonal therapy combined with chemotherapy; HT/CHT/H - hormonal therapy combined with chemo and herceptin; other TH - therapies that exclude tamoxifen. Survival rate was considered significantly different if p < 0.05.

To determine the potential influence of tumor-suppressor genes (TSGs) on the response to therapy we analyzed alterations of TP53 and PTEN genes in 90 breast tumor specimens. Namely, functional inactivation of TP53 by mutations and/or loss of heterozygosity and PTEN by loss of heterozygosity and/or promoter hypermethylation, were tested. As a result, altered TP53 gene was found in 63 out of 90 specimens (70%), while the frequency of PTEN alterations was slightly lower, 54 out of 90 (60%) patients had inactivated PTEN. At the same time, simultaneous inactivation of both TSGs was detected in 43 out of 90 tested (48%). Alterations in either one of tested TSGs were found in 31 out of 90 (34%), while 16 out of 90 (18%) had no alterations at all. Statistical analyses showed significant association of TP53 alterations with malignancy type and disease severity (Table 3). An 11-point severity scale was used to rate the severity of 16 symptoms: alopecia, anxiety, poor appetite, constipation, cough, depression, diarrhea, dry mouth, dyspnea, fatigue, nausea/vomiting, pain, peripheral neuropathy, difficulty remembering, sleep disturbances, and weakness.

Type of therapy	Cox Hazard Ratio	Significance (p value)	CI (95%)
HT vs. Oth	0.07	p<0.05	0.004 - 1.07
HT/CHT vs. Oth	1.33	<i>p</i> >0.05	0.12 - 14.70
HT/CHT/H vs. Oth	4.27	<i>p</i> =0.057	0.95 – 19.10
HT vs. HT/CHT	0.29	<i>p</i> <0.001	0.16 – 0.51
HT/CHT vs. HT/CHT/H	0.60	<i>p</i> >0.05	0.20 – 1.78
HT vs. HT/CHT/H	0.17	<i>p</i> =0.002	0.06 - 0.52

Table 2. The influence of therapy type on survival rates of persons with breast malignancy with respect to other forms of treatment

H - hormone therapy, HT/CHT - Hormone combined with chemo therapy, HT/CHT/H - Hormone combined with chemo and biological therapy, Oth - Other types of therapy

Further, Spearman's correlations revealed significant association between two analyzed TSGs (Table 3). Specifically, inactivation of PTEN was significantly more often detected in tumors with altered TP53. In addition to this, we have shown that alterations of at least one of analyzed TSGs occur more frequently in samples with severe disease status. On the other hand, wild type forms of both genes are significantly more frequent in mild disease form (Figure 2).

Survival analyses showed that TP53 alterations, as well TP53/PTEN co-alterations significantly decrease patients' survival times.

According to generated Kaplan-Meier survival curves, patients with altered TP53 gene, lived significantly shorter (p = 0.00074; Figure 3A) when compared to those with wild type (wt) gene. Survival analyses also suggest that PTEN aberrations have no influence on patients' survival rates (p = 0.7; Figure 3B) while co-alterations with p53 have (p = 0.03; Figure 3C). In other words, the survival of patients with both tumor suppressors altered was significantly shorter than the survival of those with wt genes (p = 0.024; Figure 3C).

To examine whether the outcome of different therapeutic treatments depend on inactivation of studied TSGs (separate or simultaneous), survival analyses have been done. According to our results, TP53 status has significant influence on patients' therapy response. Patients with wild type TP53 show significantly better therapy response regardless of type of therapy, compared to carriers of altered TP53 gene (Figure 3A).



Figure 2. Distribution of genetic alterations upon disease severity

(A) TP53 alterations are significantly more frequent in patients with severe disease. (B) Alterations of PTEN are also more frequent in severe disease form, although without statistical significance. (C) Wild type forms of both genes (TP53 and PTEN) are significantly more frequent in mild disease form (p < 0.01).</p>

Bivariate Spearman's correlation	Spearman's coefficient	Significance (p value)
p53 alterations/PTEN alterations	0.26	p<0.05
p53 alterations/Malignancy type	0.21	p<0.05
p53 alterations/Malignancy grade	0.11	p>0.05
p53 alterations/Severity of malignancy	0.29	p<0.01
PTEN alterations/Malignancy type	-0.02	p>0.05
PTEN alterations/Malignancy grade	0.03	p>0.05
PTEN alterations/Severity of malignancy	0.16	p>0.05

Table 3. Intercovariate Spearman's correlations





The impact of (A) TP53 alterations, (B) PTEN alterations and (C) simultaneous TP53/PTEN gene co-alterations on patients' survival rate is shown. Survival rate was considered significantly different if p < 0.05.



Figure 4. Kaplan-Meier survival curves of patients treated with tamoxifen and other TH combinations in relation to mutational status of (A) TP53, (B) PTEN and (C) both TSGs. Survival rate was considered significantly different if $p \le 0.05$.

In support of this we have shown that hormonally treated women with intact (wt) TP53 gene had significantly longer survival rate (p = 0.000001; Figure 4A) when compared to: (i) hormonally treated women with aberrant TP53 gene, (ii) women with intact (wt) p53 subjected to any of remaining three therapy combinations (HT/CHT or HT/CHT/H or therapy that exclude HT), and (iii) women with altered TP53 that belong to second (HT/CHT), third (HT/ CHT/H) or forth (systemic Th that exclude HT) therapy group. Moreover, it appeared that even those with altered TP53 gene if treated with tamoxifen only, lived significantly longer than those treated with other therapy combinations (Figure 4A, 2 vs 4, p = 0.001).

Contrary to this, no significance was found between mutational status of PTEN and treatment with tamoxifen as the main HT drug (Figure 4B, 1 vs 2, p = 0.4). Generally speaking, survival rate of HT-treated patients was almost the same regardless of PTEN status. Finally, survival rate does not depend on the mutational status of PTEN gene but it does depend on the type of subjected therapy, herein on HT-only (p = 0.00003), as shown in figure 3B and figure 4B.

In addition, the joint effect of TP53 and PTEN alterations on overall survival of breast cancer patients subjected to four different treatment regimens was also analyzed. According to generated survival curves, significant association between the type of applied therapy and simultaneous alterations of two most commonly altered TSGs in human cancers, does exist (p = 0.00001; Figure 4C). Namely, we found that women who received tamoxifen only and who had both TSGs altered lived significantly shorter than those on HT therapy with both or at least one tumor suppressor intact (Figure 4C, 1 vs 2 p = 0.03).

Finally, HT treated patients with both genes altered lived significantly longer compared to patients on other therapy regiments regardless of their TSGs status. (Figure 4C, 1 vs. 3, p = 0.02; 1 vs 4, p = 0.01).

Discussion

Tumor suppressor genes are, in general, regarded as autonomous anti-cancer genes/ proteins. However, at the molecular level, autonomy of genes/proteins appears to be a remote concept since gene expression and protein function are regulated through different cell networks, sinergistic and antagonistic ones. Therefore, linking the action of tumor suppressors may be the key to understanding and predicting their role in tumorigenesis and response to various treatment regiments. TP53 and PTEN are two most highly mutated tumor suppressors in human cancers and it is tempting to speculate that they cooperate in tumor suppression, specifically when having in mind that PTEN has been attributed to the cytoplasm while the site of action of p53 is associated with the nucleus. Consequently, the aim of our study was to investigate the impact of TP53 and PTEN inactivation on the BC response to different treatment modalities as well as their possible cooperation.

Our results reviled that TP53 mutational status has significant influence on patients' response to therapy. Namely, patients with wild type TP53 show significantly better therapy response regardless of type of therapy, compared to carriers of mutated p53 gene. This finding is expected and in concordance with some previous reports [11]. However, some recent studies reviled that patients with mutant TP53 response better to therapy, specifically to chemotherapy, due to lack of arrest in "mutant" tumors, tumors that carry mutated TP53, which results in aberrant mitoses, cell death and a superior clinical response [32]. We cannot agree less with these findings because our study unambiguously shows the opposite.

Contrary to this, we did not establish any significance between mutational status of PTEN gene alone and various treatment modalities, although the trend is unequivocal. Apparently, this contradicts our previous findings on the role of the PTEN gene in the resistance of hormone-positive breast tumors to tamoxifen [20]. We have few explanations of this contradictory. First, we think that PTEN is primarily responsible for acquired resistance, not inherent one, and will be inactivated during therapy. Secondly, and maybe more important, PTEN and p53 crossreact. Namely, quite neglected study of Freeman et al [33] showed that there is a crosstalk between PTEN and p53 tumor suppressors and that PTEN could regulate the function of WT p53 by both phosphatase-dependent and -independent mechanisms, but not mutationally altered p53. Therefore, altered p53 gets all the credits for bad response to therapy, which our results support.

The question is, what happens if p53 and PTEN are simultaneously inactivated? According to our results that is the worst scenario. We showed that patients with simultaneous inactivation of these two tumor suppressors develop resistance to all therapy regiments and live dramatically shorter compared to patients with only one gene altered or patients with WT tumor suppressor

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genes. Therefore, we suggest that mutational screening of TP53 and PTEN genes should be done previous to describing therapy regiment and, in case of observed alterations in either of these genes, particularly in both, therapy should be designed to target both PTEN and p53 or their controlled pathways.

Conclusion

Patients with wtTP53/wtPTEN showed significantly better therapy response regardless of the type of therapy, compared to carriers of altered *TP53/PTEN*. Patients with simultaneous inactivation of these two tumor suppressors develop resistance to all therapy regiments and live dramatically shorter compared to all other patients. Analysis of mutational status of *TP53* and *PTEN* is a prerequisite to the decision of therapy regiment and, in case of observed alterations in either of these genes, particularly in both, therapy should be designed to target both *PTEN* and p53, or their controlled pathways.

ber 4321-01, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Uticaj tumor supresorskih gena TP53 i PTEN na odgovor na različite načine lečenja raka dojke

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Uvod. Rak dojke (RD) je najčešći tip maligniteta i vodeći uzrok smrti od raka kod žena širom sveta. RD je izuzetno heterogena bolest i stoga su neophodni različiti modaliteti lečenja da bi se pokrile ove razlike. Cilj našeg istraživanja je bio da se ispita uticaj inaktivacije TP53 i PTEN tumor supresorskih gena (TSG) na odgovor RD na različite modalitete lečenja, kao i njihova moguća saradnja u tome, na postoperativnim uzorcima RD.

Metode. Pacijentkinje su klasifikovane, na osnovu primenjene adjuvantne terapije, u četiri različite grupe: one koje su primale samo hormonsku terapiju (HT), hormonsku terapiju u kombinaciji sa hemoterapijom (HT/CHT), hormonsku terapiju u kombinaciji sa hemoterapijom i biološkom terapijom (HT/CHT/H) i druge sistemske terapije koje isključuju HT. Funkcionalna inaktivacija TP53 i PTEN TSG je proučavana analizom mutacionog statusa, gubitka heterozigotnosti (LOH) i metilacionog statusa.

Rezultati. Naši rezultati su pokazali da je TP53 gen izmenjen kod 63 od 90 pacijenata (70%), dok je učestalost promena PTEN gena bila nešto niža, 54 od 90 (60%). Simultana inaktivacija je detektovana u 43 testirana uzorka (48%) sa značajnom povezanošću između dva analizirana TSG-a. Dalje, pokazali smo da status TP53 ima značajan uticaj na odgovor pacijenata na terapiju. Suprotno ovome, nismo pokazali značajnu asocijaciju između mutacionog statusa PTEN-a i različitih modaliteta lečenja. Međutim, utvrđena je značajna povezanost između primenjenih terapija i simultanih inaktivacija ova dva TSG-a (p = 0,00001).

Zaključak. Pacijenti sa wtTP53 pokazuju značajno bolji terapijski odgovor bez obzira na vrstu terapije u poređenju sa nosiocima mutiranog TP53 gena.

Ključne reči: rak dojke, p53, PTEN, adjuvantna terapija



Original article

Deaf and technology: A bibliometric analysis of scientific literature

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Summary

Introduction. Technology has the potential to reduce isolation, increase independence, provide educational, financial and social opportunities for users, but there may still be barriers, especially for people with disabilities or sensory deficits. Therefore, it is very important to determine what science has been dealing with in this area, more precisely in the area of the deaf. The main aim of this paper was to map the progress and trends of scientific literature in the field of technology for the deaf (children and adults).

Methods. A bibliometric analysis in VosViewer was performed to determine the set goals. The Dimensions database was chosen for literature analysis. The unit of analysis consisted of 1242 publications and VosViewer was applied.

Results. The results show that this topic in science has experienced exponential growth in the last decade. Also, the most productive authors, journals, institutions and countries, as well as their collaboration network, were identified through a visual analysis of co-citations. Based on the analysis of co-words, we can draw a conclusion that the words: student, sign language, cochlear implant, classroom, parent, outcome are the most frequently repeated words, which would mean that the topics covered in this domain are mainly focused on children and their functioning in the environment and school system.

Conclusion. Providing the main lines of research generated in this field allows scientists to follow the trends themselves. Also, therapists can use our analysis to identify sources that can indicate how and in what context deaf children can use technology.

Key words: deaf, technology, VosViewer

Introduction

In a modern society, every person is surrounded by technological achievements. Kaye believes that technology has the potential to reduce isolation, increase independence, provide educational, financial and social opportunities for users, but there may still be barriers, especially for people with disabilities or sensory deficits [1]. The fact is that the progress of technology is taking place rapidly, while bringing new forms of communication into the daily life of an individual. Our daily life activities and interactions with other people have been radically changed in terms of new forms of communication (eg. smart phones with a wide range of applications).

As a result, we have a situation where people spend much more time communicating through these media than face to face [2]. New ways of communication are based mainly on written communication, through text messages, as well as, multimedia content. On the other hand, oral communication is a key difficulty for the deaf, which can cause additional problems. Namely, clinicians and researchers agree that access to communication at home, at school and with peers is important for the linguistic, cognitive and socioemotional development of deaf children [3, 4, 5]. Deaf children use different ways to communicate with their hearing community. Such a model that incorporates the use of all forms of communication in order to achieve interaction with the environment is called total communication. Thus, Purwowibowo believes that the total communication learning model has the potential to improve their language capacity in terms of speaking, writing and reading [6]. This model enables deaf children to learn new words and their meanings, as well as, to communicate in society. However, we should be mindful of the fact that the main method of communication for deaf children is sign language. However, using only this method the deaf can remain completely isolated from the hearing community. Therefore, Arthur claims that "technology is extremely promising for people with disabilities", and that new technologies can bring new opportunities to bridge the gap between deaf people and the hearing community [7]. Even the classroom has changed significantly compared to a few decades ago. The introduction of computers in the education of the deaf in 1980 made a big change. Now, along with smart boards, laptops, educational websites and online learning tools, students very often have their own technology (smartphones, tablets) with which they have been familiar since the youngest age [8]. Deaf children have learned to communicate at a distance without reading the interlocutor's mouth. Before that, deaf people could

not imagine communicating with someone who was not in their vision field. Dunham hypothesized that technological progress in the field of deafness would have three directions: hearing aids, communication technology, and brain research in cochlear implanted children [9]. Therefore, this paper focuses on the evolution and trends of scientific publications on the mentioned topic. An initial search of the Dimensions database did not find any papers on a similar topic, so the aim of this paper is to:

- 1) to determine the progress of scientific literature on the topic of deaf- technology;
- determine the most relevant aspects of this topic and the relevant journals;
- determine the most productive authors, institutions and countries as well as their network of collaboration.

Methods

This paper dealt with bibliometric analysis of scientific literature on the topic of deaf and technology. For this purpose, the Dimensions database was chosen. Mapping of scientific publications and their analysis was done in the VosViewer program, intended for bibliometric and visual data analysis. The advantage of this methodology is in the quantitative and comprehensive evaluation of scientific literature [10]. In order to reduce the researcher's bias, the analysis procedure protocol was established [11]. The research design is based on the analysis of co-words. Also, the different performances of the program allowed the generation of maps with nodes in order to answer the research questions.

Bibliometric and visual analysis was used to map the scientific literature in the field of deaf-technology. The Dimensions database was used for the search. Publications are collected using the following search strategy: deaf AND technology. The search is refined by: DOCU-MENT TYPES: (ARTICLE). The search was conducted in September 2022 and a total of 1242 articles were found. Articles with the words deaf and technology in the title or abstract in all research categories were included. The research covers all citation databases, without an exact time frame. Exclusion criteria were studies that include additional difficulties other than hearing impairment (eg deaf-blindness). Figure 1 shows the flowchart according to the PRISMA protocol, which consists of the phases that were carried out during the research.



Figure 1. Flowchart according to PRISMA

Results

At the figure 2 we see the evolution of scientific production on this topic from almost five decades ago to today. This evolution had two clearly defined periods, the first from 1978–2007 where the number of publications was very small and the second from 2007 to the present day where scientific production grew exponentially, reaching its peak in 2021.



Figure 2. Evolution of scientific production



Figure 3. The most dominant research categories

At figure 3, we see research categories that have more than 50 published articles in this area. As we can see, the analyzed articles are mainly from the fields of medicine and health sciences, education, language and communication, as well as information sciences.

Looking at table 1, we see five journals that mostly dealt with this topic. Thus, we notice that the journal *American annals of the deaf* had the most articles (n = 81) on this topic, and is followed by *The journal of deaf studies and deaf education* (n = 30). However, if we look at column three in table 1, we will notice that the most cited journal is *The journal of deaf studies and deaf education,* followed by *American annals of the deaf.*

Journals	Number of documents	Citations
American annals of the deaf	81	682
The journal of deaf studies and deaf education	30	715
Sign language studies	16	112
Universal access in the information society	13	203
International journal of pediatric otorinolaringology	13	300

The journal co-citation map shown in figure 4 gives us an overview of the structure of the scientific world. Journal clusters can be identified on the map. Clusters that are closer together on the map indicate close association. As we can see in the figure 4, we have four large clusters. Interpretation of the map is simple. The left side of the map contains three clusters (yellow, green and purple). The yellow cluster refers to neuropsychological sciences, while the green one refers to the field of public health. The purple cluster refers to the field of otorhinolaryngology. The lower part of the map is a blue cluster that refers to the areas of language, hearing and special education. The right part of the map is a red cluster related to computer science and assistive technology. From the map, we clearly see the relationship of all clusters, that is, we see that all areas that deal with this topic are very closely and tightly connected, except for assistive technology, which is very weakly connected to other areas dealing with deaf and technology.



*Note: The size of the circle is directly proportional to the number of publications of a particular journal, and the closeness of the circles and the thickness of the lines are proportional to the frequency of citations.

Figure 4. Journal co-citation map

In table 2, we see the three most cited articles in the field of deaf-technology. The most cited article is by Dermott from 2004. The author concluded that people with cochlear

implants, people with cochlear implants and hearing aids, perceived music better than people who used only hearing aids.

Table 2. The most cited articles in our unit of analysis	
McDermott HJ. Music perception with cochlear implants: a review. Trends Amplif 2004;8(2):49–82.	383
Wilson BS, Dorman MF. Cochlear implants: a remarkable past and a brilliant future. Hear Res 2008;242(1-2):3–21.	237
Lederberg AR, Schick B, Spencer PE. Language and literacy development of deaf and hard-of-hear- ing children: successes and challenges. Dev psychol 2013;49(1):15–30.	216

Authors	n	Citations
Huenerfauth, Matt	10	81
Kushalnagar, Poorna	9	270
Mayer, Connie	7	173

Table 3. The most productive authors

Table 4. Countries that were most productive indeaf-technology filed of science

Countries	n	Citations
USA	336	5042
United Kingdom	68	1242
Canada	40	452
Australia	40	1206
Brazil	39	130

The countries with the most publications in this field are the United States of America. Other countries are far behind them.In the third column, we see that the most quoted, as expected to be, is the USA, followed by the UK and immediately behind them is Australia. The least cited publications are from Brazil (Table 4). Figure 5 shows the bibliographic coupling of countries, where we see that the USA is in the center of the map, as is expected. Otherwise, the term bibliographic coupling refers to the situation when two documents cite one or more in common. Thus, we see that in this sense, countries with more publications (which circles are larger) have stronger connections,



*Note: The size of the circle is directly proportional to the number of publications of a certain country, and the closeness of the circles and the thickness of the lines are proportional to the strength of the bibliographic coupling.

Figure 5. Map of bibliographic coupling of countries

so the USA has the strongest connections with Canada, Australia and the UK, while of course, in this sense, they are also connected with other countries, but those connections are weak.

In table 5, we see that the leading institution in this field is the Rochester Institute of Technology. Rochester Institute of Technology is a private research university in the city of Henrietta in Rochester, New York metropolitan area.

Table 5. Leading organizations in the field of deaftechnology

Name of the institution	n
Rochester Institute of Technology	48
Galaudet University	34
University of Melbourne	14
University of Washington	12

At figure 6, we see a network of co-words. We notice separated four clusters (marked in red, blue, green and yellow). The larger the nodes, the more often the words are repeated. The wider the lines between the nodes, the more noticeable the connections, the topics are closer, so we see that in the green cluster we have words that mainly refer to technology in terms of hearing aids, in the red cluster we see words that refer to the barrier that deaf people havein society, the blue cluster refers to sign language, while the yellow cluster refers to the use of technologies in the educational system.



*Note: The larger the nodes the more often the word is repeated;nodes of the same color represent words that appear together most often.

Figure 6. Map of word co-occurrences

Discussion

Considering that recently bibliometric analysis has been used to examine the trends and progress of the scientific literature in different research categories, the aim of our analysis was to examine different dimensions of deaf-technology search, which includes productivity trend, leading research categories, organizations, journals and authors, as well as the most frequently treated topics. It is well known that we live in a society characterized by the continuous advancement of technology. Innovative technological achievements have spread in all spheres of life [12]. Considering that, there was a need to examine the relationship between deafand technology in literature. Until now, it is known that technology covers a wide range of assistive, adaptive and rehabilitative devices for people with special needs. During the last 15 years we have seen a huge development in the field of deaf and technology [13], which coincides with the research dynamics in this area, as evidenced by our analysis. Namely, it was established that since 2008, scientific production in this area has grown exponentially. Technology, which mainly refers to assistive technology, is divided into hardware, software and hearing aids. The main purpose of these devices is for deaf people to overcome the basic difficulty they have, that is, difficulty in communication. Noemi, in her research about autism and technology, also found sudden increase in scientific literature since 2009, which was explained by sudden increase in technological achievements in the social sphere, which also crossed over into other fields, such as the use of technology for therapeutic purposes or purposes of assistive technology [14]. Also, we see the biggest increase in the last three years, which is expected, given the dominant form of distance learning (online) during the Covid-19 pandemic. So the subject of the researcher must have been to find the best practical solutions so that the deaf could follow the class.

The most productive research category on this topic is medical and health sciences, followed by education, language and communication as well as information sciences, which is expected, considering that according to the WHO (2015), there are 360 million people worldwide (over 5% of the world's population) with hearing impairment, of which 32 million are children, so it is primarily a health problem [15]. Among the various sources that share knowledge on this topic with the scientific community, the most productive is the American Annals of the Deaf, with the highest number of publications. Other journals, such as The journal of deaf studies and deaf education, have much fewer publications, but surprisingly more citations. So, these are the two leading journals in this field, which is not surprising considering that the country with the most published publications is the USA where those originate. USA is also in the center of the bibliographic coupling map, with the closest connections with Canada, Australia and the UK. Although Brazil is also one of the five most productive countries, obviously the relationship between these two countries is not so close in this sense. Furthermore, the analysis showed that the most productive authors are Matt Huenerfauth, from the Rochester Institute of Technology, which is also a leading organization in this field, and Poorna Kushalnagar, from Gallaudet University, which is again consistent with the findings of the leading institutions, considering that this organization is right after the Rochester Institute for technology. However, the most cited author is Poorna Kushalnagar, whose fields of interest are deaf communication and the quality of life of hearing-impaired people. When it comes to the word co-occurrence map, we see that the words that appear mostly next to the keywords are: student, sign language, cochlear implant, classroom, parent, outcome, which would mean that the topics covered in this domain are mainly focused on children and their functioning in the environment and school system.

Conclusion

Our analysis has theoretical and practical implications. Theoretical implications refer to the fact that our results will be useful to future researchers in collecting adequate and interesting sources from this field of research. Also, knowing the main lines of research generated in this field allows scientists to follow the trends themselves. In this case, they do not need to check what has been previously pub-

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lished; thanks to this research, they can know what current topics they can cover. Among the practical implications is the fact that therapists or teachers can use our analysis to identify sources that can indicate how and in what context deaf children can use technology. Limitations of our study relate to the limitation of the search to one database, Dimensions. A recommendation for further research could be to extend the unit of analysis to other databases such as Wos, Scopus, and Pubmed.

was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Gluvi i tehnologija: Bibliometrijska analiza naučne literature

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Uvod. Tehnologija ima potencijal da redukuje izolaciju, poveća nezavisnost, omogući obrazovne, finansijske i socijalne prilike za korisnike, ali ipak mogu postojati i prepreke, pogotovo za osobe sa teškoćama ili senzornim deficitima, stoga je veoma važno utvrditi čime se do sada nauka bavila u ovoj oblasti, preciznije u oblasti gluvih. Cilj ovog istraživanja bio je mapirati napredak i trendove naučne literature u oblasti primjene tehnologije kod gluvih osoba (djece i odraslih).

Metode. Korišćena je bibliometrijska analiza kako bi se utvrdili postavljeni ciljevi. Za analizu literature izabrana je baza podataka Dimensions. Jedinica analize se sastojala od 1242 publikacije i primijenjen je program VosViewer.

Rezultati. Rezultati su pokazali da je ova tema u nauci doživjela eksponencijalni rast posljednju deceniju. Takođe, identifikovani su najproduktivniji autori, časopisi, institucije i zemlje, kao i njihova mreža saradnje kroz vizuelnu analizu kocitiranja. Na osnovu analize riječi koje se ponavljaju možemo da zaključimo da su riječi: učenik, znakovni jezik, kohlearni implant, učionica, roditelj, ishod, riječi koje se najčešće ponavljaju, što bi značilo da su teme koje su obrađivane u ovom domenu uglavnom fokusirane na djecu i njihovo funkcionisanje u okolini i školskom sistemu.

Zaključak. Poznavanje glavnih pravaca istraživanja generisanih u ovoj oblasti omogućava naučnicima da sami prate trendove. Takođe, terapeuti mogu koristiti našu analizu u cilju identifikacije izvora koji može ukazati na to kako i u kom kontekstu gluvi mogu koristiti tehnologiju.

Ključne riječi: gluvi, tehnologija, VosViewer



Original article

Visual-motor integration of younger school-aged children

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Summary

Introduction. Visual-motor integration (VMI) is defined as the degree to which visual perception (VP) and finger-hand movements are well coordinated. The VMI consists of two components: VP and motor coordination (MC). The main goal of our research was to determine whether there are differences in age and gender categories in VMI, VP and MC scores, as well as whether there is a correlation between VMI and school success of younger school-aged children.

Methods. Out of 103 student respondents, 52 were female (50.5%), aged 6 to 11 years (8.05 \pm 1.44 years), divided into two groups according to age: 6–8 years (first, second and third grade) and 9–11 years (fourth to fifth grade). Data on the level of VMI were obtained by applying the following tests: Beery-Buktenica Developmental Test of VMI, VP test and MC test.

Results. In the older age group of subjects, a significant difference was observed in the mean values of the score on the VMI (12.67 \pm 1.92), VP (23.69 \pm 3.21) and MC (24.34 \pm 3.23) tests comparing to the younger group of subjects (9.98 \pm 2.12; 20.80 \pm 3.2; 19.65 \pm 3.82) (p < 0.001), while the difference in the mean values of scores in relation to gender was not observed. A significant, positive and strong correlation was observed between the scores on the VMI, VP and MC test with the success of second to fifth grade students (p < 0.050).

Conclusion. Given such a strong correlation between VMI and the success of younger students, we conclude that it is important that VMI disabilities are identified in time, so that these students can be referred for further assessment and receive the necessary support.

Key words: younger school age, visual-motor integration, visual perception, motor coordination

Introduction

Visual-motor integration (VMI) is defined as the degree to which visual perception and finger-hand movements are well coordinated [1]. VMI represents the ability to connect a motor output to a visual input [2]. This ability refers to the complex process of integrating visual and motor information in order to achieve the most precise movement with the least possible consumption of energy and time [2, 3]. Visual-motor integration is influenced by various factors, such as psychological and/or health-medical factors, and environmental conditions. Thus, children who have such disturbances or difficulties, or unfavorable environmental conditions, show worse results than their peers on the Beery-Buktenica developmental test of VMI. The authors also state that the construct of VMI is composed of two components: visual perception (VP) and motor coordination (MC), but that this construct cannot be viewed only as a simple sum of these two areas, rather as a separate entity. These two parts may function well independently, but not in a combination. Therefore, in addition to the test of VMI, two supplemental tests are performed: the test of VP, and the test of MC [1].

The first component of VMI is VP. Visual perception is defined as the process by which individuals assign meaning, understanding and interpretation to what they have seen, that is, it represents an intermediate step between a simple visual sensation and cognition [4]. Visual perception refers to the process of organizing and deciphering visual information [5]. VP skills are often assessed in children, because they are related to school readiness and school success in reading, mathematics and writing, especially at a younger school age [5].

The second component of VMI is MC. Motor development of children is directly related to the maturation of the child, and it begins from the first day of life. This development depends on the maturation of the central nervous system, the proper development of body structures and sensory systems [6]. During the early stages of motor learning, movements are inaccurate and largely dependent on feedback [2]. Movements become more complex over time and children's coordination of movements develops. Children with underdeveloped fine motor coordination may have problems in achieving harmonious writing and rewriting [7].

Difficulties in VMI cause problems in acquiring academic skills, participating in school activities, social relations and self-concept [8]. These difficulties are reflected in writing, drawing, following lines while reading, navigating maps and charts and other school activities [9]. It has also been shown that the ability of VMI is less developed in children with writing problems compared to peers who do not have these problems, and that difficulties of VMI have been shown to predict handwriting legibility and writing speed [10]. Children of younger school age may have writing problems due to difficulties with VMI, and the most common problems are: incorrect letter formatting, poor alignment, reversals, uneven letters size, irregular spacing between letters and words and slow motor speed [11]. Many authors also emphasize the importance of these abilities for other academic skills, especially emphasizing the importance of VP for reading [12, 13]. Accordingly, and given that we have a very small number of papers dealing with this topic, our paper will try to provide answers about the level of development of VMI among younger school-aged children. Based on the above, the main goal of our research was to determine whether there were differences in age and gender categories in VMI, VP and MC scores, as well as whether there was a correlation between VMI and school success of younger schoolaged children.

Methods

This cross-sectional study was conducted in the elementary school "Vuk Karadžić" in Vlasenica (Republic of Srpska, Bosnia and Herzegovina) in September 2021. Testing of the examinees was performed individually in an empty classroom, in order to enable peaceful conditions for uninterrupted work.

The Beery-Buktenica Developmental Test of VMI was used in our research (VMI 6th Edition, Beery KE and Beery NA, 2010). It is usually used for screening purposes to identify difficulties in visual-motor integration, and can also be used for research purposes. The test tasks consist of copying geometric forms and can be applied individually or in groups in just 10–15 minutes. In our research, we used three subtests of VMI.

The VMI test has 15 tasks, which consist of 15 geometric forms arranged in developmental order, from simpler to more complex. It assesses the extent to which individuals can integrate visual and motor abilities. Examinees were asked to copy the given forms in the marked fields below each given form. Each correctly done task carries one point, and the total number of points is 15. The test is not limited in time, but the test is ended if the examinee incorrectly copies three given forms in a row.

The VP test consists of 30 tasks arranged in complexity, from more simple to more complex. It assesses individual's visual perception when not integrated with fine motor coordination. In order for this test to be as focused as possible on visual-perceptual tasks, motor tasks are reduced to a minimum, that is, examinees only need to choose their answer among the offered figures. Each correct answer carries 1 point. The total number of points is 30, and the time allowed to solve these tasks is 3 minutes. Testing is stopped after 3 minutes, as well as when the examinee makes three consecutive errors.

The MC test consists of 30 tasks and evaluates fine motor skills when not integrated with visual perception. Examinees need to draw simple geometric shapes in the space provided, first connecting the dots, then without dots, and finally, to draw complex shapes in the space which size is progressively decreasing without crossing the borders. One point is awarded for each correctly completed task. The maximum number of points is 30. The test is limited in time and the allowed time for this test is 5 minutes.

In the research we used the methods of descriptive and analytical statistics. Among the methods of descriptive statistics, measures of central tendency and measures of variability were used, namely: arithmetic mean with standard deviation, as well as relative numbers for categorical variables. Among the methods of analytical statistics, parametric methods were used to assess the significance of the difference between three or more groups, namely one-factor analysis of variance (ANOVA). In case of deviation from the normality of the distribution, a non-parametric alternative Kruskal-Wallis U test was used with additional Dunn-Bonferroni post hoc analysis. The Mann-Whitney U test was used to assess the significance of the difference between the two groups of subjects. For the correlation analysis, Pearson correlation analysis was used. SPSS software package version 21.0 (Statistical Package for Social Sciences SPSS 21.0 Inc, USA) was used for statistical data processing.

Results

The sample consisted of 103 students of both genders. Distribution of students/respondents in regard to socio-demographic parameters, as well as overall and area specific children's success are represented in table 1. Mean age of the students was 8.05 ± 1.44 years.

Figure 1 shows the mean values of the VMI, VP and MC scores in relation to the gender and age of the respondents. There was no statistically significant difference in the mean

Socio-demographic characteristics	n (%)
Gender	
Male	51 (49.5)
Female	52 (50.5)
Age, years	
From 6 to 8	60 (58.3)
From 9 to 11	43 (41.7)
Grade	
First	20 (19.4)
Second	22 (21.4)
Third	18 (17.5)
Fourth	22 (21.4)
Fifth	21 (20.4)
School success – II grade	
Subject area – my environment	
Participates	0 (0.0)
Successful	3 (13.6)
Extremely successful	19 (86.4)
Subject area – speech, expression and	
creation	
Participates	0 (0.0)
Successful	2 (9.1)
Extremely successful	20 (90.9)
Subject area – sport, rhythmics and music	
Participates	0 (0.0)
Successful	0 (0.0)
Extremely successful	22 (100.0)
School success – III, IV and V grade	
Insufficient	0 (0.0)
Sufficient	0 (0.0)
Good	5 (8.2)
Very good	14 (23.0)
Excellent	42 (68.9)

 Table 1. Socio-demographic characteristics of respondents

values of the VMI, VP and MC scores between girls and boys. A high statistically significant difference in the mean values of the VMI score was observed between the respondents of the younger and older age groups (p < 0.001). The older age group of examinees (12.67 ± 1.92) had significantly higher mean values of the VMI score compared to the younger age group (9.98 \pm 2.12). The older age group of subjects (23.69 \pm 3.21) had significantly (p < 0.001) higher mean values of VP score compared to the younger age group (20.80 ± 3.21) . The older age group of subjects (24.34 ± 3.23) had significantly (p < 0.001) higher mean values of MC score compared to the younger age group (19.65 ± 3.82) (Figure 1).

Figure 2 shows that there is a high statistically significant difference in the mean values of the VMI score between the groups of respondents divided in relation to the grade. Subjects attending the fifth grade (13.28 ± 1.73) had statistically significantly higher mean values of VMI score compared to respondents attending the first (8.90 ± 2.40) (p < 0.001), second (10.04 ± 1.83) (p < 0.001) and third grades (11.11 ± 1.52) (p < 0.001). Examinees attending the fourth grade (12.09 ± 1.94)



Figure 1. Mean values of subtests of visual-motor integration, visual perception and motor coordination between respondents divided in relation to gender and age

M - mean; SD - standard deviation; Mann-Whitney U test; ***p < 0.001



Figure 2. Mean values of subtests of visual-motor integration, visual perception and motor coordination between respondents divided in relation to grade

M - mean; SD - standard deviation; Analysis of variance (ANOVA), Tukey post hoc test; ***p < 0.001

had higher mean values of this score in relation to the examinees of the first and second grade (p < 0.001). There was a high statistically significant difference in the mean values of the VP score between the groups of respondents divided in relation to the class. Subjects attending the fifth grade (24.47 ± 3.29) had significantly higher mean values of the VP score compared to the subjects attending the first (19.35 ± 3.75) (p < 0.001), the second (21, 22 ± 2.77) (p < 0.001) and third grades (21.88 ± 2.58) (p < 0.001). Also, the examinees attending the fourth grade (22.95 ± 3.03) had significantly higher mean values of this score in relation to the examinees of the first grade (p < 0.001). Subjects attending the fifth grade (25.04 ± 3.21) had significantly higher mean values of MC score compared to examinees attending the first (17.90 ± 3.99) (p < 0.001), second ($19, 95 \pm 3.59$) (p < 0.001) and third grades (21.22 ± 3.26) (p < 0.001). Also, it was noticed that the examinees attending the fourth grade (23.68 ± 3.18) had higher mean values of this score in relation to the examinees of the first and second grades (p < 0.001) (Figure 2).

Subject area	Subtests of visual-motor integration	Evaluation of subject area (M±SD)		p (MW)
		Successful	Extremely successful	
My environment	Subtest of VMI	7.66±1.52	10.42±1.60	0.021
	Subtest of VP	18.00 ± 4.58	21.73±2.15	0.026
	Subtest of MC	16.33±3.78	20.52±3.30	0.058
Speech. expression and creation	Subtest of VMI	7.50±2.12	10.30±1.65	0.036
	Subtest of VP	17.50±6.36	21.60±2.18	0.043
	Subtest of MC	15.50±4.94	20.40±3.26	0.064

Table 2. Mean values of the visual-motor integration scores between groups of second-grade students divided according to success in the subject areas of my environment and speech, expression and creation.

M - mean; SD - standard deviation; VMI - visual-motor integration; VP - visual perception; MC - motor coordination; MW - Mann-Whitney U test; ***p < 0.001

Table 2 shows the mean values of the VMI scores between groups of second-grade students divided according to success in the subject areas of my environment and speech, expression and creation. It was noticed that the respondents who are extremely successful (10.42 ± 1.60) in the subject area of my environment have significantly (p = 0.021) higher mean values on the VMI score compared to respondents who are successful in this subject area (7.66 \pm 1.52). Also, extremely successful (21.73 ± 2.15) students had significantly (p = 0.026) higher mean scores on the VP test compared to successful students in this subject area (18.00 ± 4.58) . The difference in the mean values of the MC score between the groups of examinees divided according to success in the subject area *my environment* was not observed. It was noticed that the respondents who are extremely successful (10.30 ± 1.65) in the subject areas of speech, expression and creation had significantly (p = 0.036) higher mean scores on the VMI test compared to respondents who are successful in this subject area $(7.50 \pm$ 2.12). Also, extremely successful (21.60 ± 2.18) students had significantly (p = 0.043) higher mean scores on the VP test compared to students successful in this subject area (17.50 \pm 6.36). The difference in the mean values of the MC score between the groups of examinees

divided according to success in the subject area of *speech*, *expression* and *creation* was not observed (Table 2).

Figure 3 shows that excellent students of the third, fourth and fifth grades had a significantly (p < 0.001) higher VMI score (13.09 ± 1.33) compared to very good (10.28 ± 1.32) and good students (10.20 ± 2.48). Also, excellent students of the third, fourth and fifth grades had a statistically significant (p < 0.001) higher VP score (24.61 ± 2.05) compared to very good (19.78 ± 2) and good students (20.40 ± 4.09), and excellent students of the third, fourth and fifth grades had a significantly (p < 0.001) higher MC score (25.00 ± 2.52) compared to very good (20.14 ± 2.87) and good students (19.40 ± 3.13) (Figure 3).

Pearson's correlation coefficient showed the existence of a highly statistically significant (p < 0.001) positive and strong correlation between all scores of VMI. Highly statistically significant, positive and strong correlation was observed between the scores of VMI and the VP with the success of second grade students in the subject area my environment (r = 0.526; p < 0.010; r = 0.473; p < 0.050), the success of second grade students in the subject area of *speech*, *expression* and *creation* (r = 0.448; p < 0.050; r = 0.435; p < 0.010) and general school success of third, fourth and fifth grades students (r =





Success in a school of III, IV and V grade students

Figure 3. Mean values of the visual-motor integration scores between groups of third, fourth and fifth grade students divided according to success in school

M - mean; SD - standard deviation; Kruskal-Wallis U test, Dunn-Bonferroni post hoc; ***p < 0,001

Success of II grade Success of Success of II III, IV and Visual-mo- Visual Motor students in subject grade students in tor integra- perception coordination area "speech, V grade subject area "may expression and students in tion score score score environment" creation" school Visual-motor integration score Visual perception 0.865*** score Motor coordina-0.929*** 0.763*** tion score Success of II grade students in subject 0.526** 0.473* 0.410** area "may environment" Success of II grade students in subject area "speech. 0.448^{*} 0.435** 0.401 0.796*** expression and creation" Success of III IV 0.583*** and V grade stu-0.632*** 0.622*** 0.638*** 0.511** dents in school

Table 3. Correlation between scores of visual-motor integration, visual perception and motor coordination with school success of second, third, fourth and fifth grade students

Pearson's correlation coefficient (r) was used, the level of statistical significance p <0.05, r values are shown in the table; *p < 0.05, **p < 0.01, ***p < 0.001
0.632; p < 0.001; p = 0.622; p < 0.001). Also, it was noticed that the correlation between the MC score and the success of second grade students in the subject area *my environment* (r = 0.410; p < 0.010), and general school success of third, fourth and fifth grades students (r = 0.638; p < 0.001) was strong, positive and statistically significant, while a significant correlation between the MC score with the success of second grade students in the subject area of *speech*, *expression* and *creation* (r = 0.401; p > 0.050) was not observed (Table 3).

Discussion

The goals of our research were to determine the level of development of VMI ability of younger school-age students and whether there were differences in achievements on VMI, VP and MC tests between the students divided into groups according to gender, age and school success. The results showed that fifth grade students had significantly higher average values (p < 0.001) on the VMI test compared to first, second and third grades students, as well as fourth grade students compared to first and second grade students. In Brazilian study, which included 50 students of younger school age, ie, ages 6-11, fourth grade students achieved the highest average number of points on the VMI test and fourth grade students had significantly higher mean values (p < 0.001) on the VMI test compared to first and second grades students [11]. In our research, fifth-graders proved to be the most successful on VMI, VP and MC tests, while in the Brazilian study, fourth-graders achieved the best results on all three tests [11]. First grade students of the mentioned Brazilian study performed worse than the students of the older grades on the VMI, VP and MC tests [11], as shown in our research. Apart from being the youngest, one of the reasons why the first grade students in our study achieved such low results may be that our research was

conducted in September, ie at the very beginning of the first grade, and there is a possibility that these students were not adapted enough to the new environment.

In our study, we found that in the older age group of subjects a significant difference (p < 0.001) was observed in the mean scores on the VMI, VP and MC tests compared to the mean scores of the younger group of subjects. From these results we see that VMI, VP and MC progresses with age of the child. In the study by Radovanović et al. [9], conducted in Serbia, in order to determine the differences in achievement on VMI, VP and MC tests between deaf and children with hearing impairment, and children of typical development, it was found that children of typical development of the older age group achieved better results on all three tests compared to younger age group respondents. However, these differences did not prove to be statistically significant, which the authors explained by the complex relationship between age and the development of VMI; the correlation was not linear [9]. Ercan et al. [8] conducted a study on a sample of 148 children aged 5 and 6 years in order to determine the impact of age and socio-economic status on the VMI. The results of this Turkish study showed that a group of older respondents achieved better results than younger respondents on the VMI, VP and MC tests. These results were statistically significant, which proved that the development of VMI, VP and MC abilities of children dictates with age [8], which was confirmed by the results of our study. Differences in achievement in the VMI test in terms of students age were also found in a 2014 study conducted by Harmanci Baskut [14] in Turkey. This study involved 87 first graders, ages 5 to 7. Students of the older age group achieved statistically significantly better results compared to the younger age group on the VMI test [14], which is in line with the results of our research.

We found that no statistically significant difference was observed in the mean scores

on the VMI, VP, and MC tests between girls and boys. These results are in line with the results of the previously mentioned research by Radovanović et al. [9], also by Duiser et al. [15], Van Wyk et al.[16], Harmanci Baskut [14] and Coetzee et al [17].

In our study, Pearson's correlation analysis determined a highly statistically significant, positive and strong correlation between scores on VMI and VP tests with the success of second grade students in the subject area my environment, in the subject area speech, expression and creation and with general school success of third, fourth and fifth graders. In 2003, Sortor and Kulp [18] demonstrated the significant correlation between these abilities and success in mathematics and reading, especially emphasizing the role of VP, and concluded that in children with poor performance in mathematics and/or reading, further assessment of VP should be made [18]. The results of a recent study conducted in Australia in 2019 are also consistent [19]. The study, which included 222 second-grade elementary school students in Brisbane showed a significant correlation of VMI with students success [19]. The correlation of these abilities with the success of younger school age children was also proved by the results of the South African study from 2020 on a sample of 863 students

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of mean age $(9.9 \pm 0.42 \text{ years})$ [20], and the significant correlation of the abilities of VMI, VP and MC with success in mathematics, reading and writing was also proven in a recent study published in 2022 [21].

Conclusion

The results of numerous studies conducted around the world [16, 17, 19], have shown that VMI is better developed in older children, that there is no difference in gender and that VMI is necessary for basic academic skills: reading, writing and arithmetic [18, 19, 21], which was partially evidenced by the results of our research. Given such a strong correlation between VMI and achievement of students in school, it is clear that it is important that VMI disabilities are identified in a timely manner, so that these students can be referred for further assessment. It is well known that elementary school acquires knowledge that forms the basis for higher levels of education, and that school success is taken as a condition for enrollment in higher education. Therefore, a timely assessment of VMI is necessary in order to create an adequate stimulation program immediately after the detection of difficulties.

obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Vizuo-motorna integracija djece mlađeg školskog uzrasta

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Uvod. Vizuo-motorna integracija (VMI) se definiše kao stepen u kome su vizuelna percepcija (VP) i pokreti prstiju i šake dobro koordinisani. Konstrukt VMI je sastavljen iz dvije komponente, i to VP i motorne koordinacije (MC). Osnovni cilj našeg istraživanja bio je da utvrdimo da li između učenika različitog uzrasta i pola postoje razlike u skorovima VMI, VP i MC, kao i da li postoji povezanost između VMI sa školskim uspjehom djece mlađeg školskog uzrasta.

Metode. Od 103 ispitanih učenika, 52 je bilo ženskog pola (50,5%), uzrasta od 6 do 11 godina (8,05±1,44 godina), podijeljenih u dvije grupe s obzirom na uzrast: 6–8 godina (prvi, drugi i treći razred) i 9–11 godina (četvrti i peti razred). Podatke o nivou VMI dobili smo primjenom testova: Beery-Buktenica razvojnim testom VMI, testom VP i testom MC.

Rezultati. Kod starije uzrasne grupe ispitanika uočena je značajna razlika u prosječnim vrijednostima skora na testu VMI (12,67±1,92), VP (23,69±3,21) i MC (24,34±3,23) u odnosu na mlađu grupu ispitanika (9,98±2,12; 20,80±3,2; 19,65±3,82) (p<0,001), dok razlika u prosječnim vrijednostima skorova u odnosu na pol nije uočena. Uočena je statistički značajna, pozitivna i jaka korelacija između skorova na testu VMI, VP i MC sa školskim uspjehom učenika drugog, trećeg, četvrtog i petog razreda (p<0,050).

Zaključak. S obzirom na ovako jaku povezanost VMI sa uspjehom učenika mlađeg školskog uzrasta, zaključujemo da je važno da smetnje VMI budu prepoznate na vrijeme kako bi se ovi učenici uputili na dalju procjenu i dobili potrebnu podršku.

Ključne riječi: mlađi školski uzrast, vizuo-motorna integracija, vizuelna percepcija, motorna koordinacija



Original article

Stereological analysis of vascular network of subcortical auditory centers

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Summary

Introduction. Subcortical auditory centers have several sources of blood supply. Cochlear nuclei are vascularized by the anterior inferior cerebellar artery. Superior cerebellar and posterior cerebral arteries supply the inferior colliculus nucleus, while the medial geniculate body nucleus is supplied by several posterior cerebral artery branches. The aim of the research was to quantify the vascular network of subcortical auditory centers.

Methods. Twelve adult brains, both sexes, aged 21 to 78 years, without signs of neurological diseases were analyzed in this study. Samples for histological sections, stained by the Mallory method, were obtained from strata cut at levels: the junction of the middle and rostral thirds of the oliva, the inferior colliculi, and the thalamic pulvinar. Volume, surface, and length density of the vascular network of subcortical auditory centers were analyzed stereological parameters.

Results. All parameters had the highest values in the medial geniculate body nucleus. Statistically significant difference was found in the volume, surface, and length density between vascular networks of the cochlear nuclei and medial geniculate body nucleus, and between inferior colliculus nuclei and medial geniculate body. Vessels in cochlear nuclei and inferior colliculus nuclei differed only in length density.

Conclusion. Cochlear nuclei and inferior colliculi nuclei blood vessels have a similar density and diameter, but vessels in inferior colliculi nuclei are more tortuous. In the medial geniculate body nucleus vessels are larger, denser and more tortuous compared to the other two subcortical auditory centers.

Keywords: cochlear nuclei, inferior colliculi, medial geniculate body, blood vessels

Introduction

The most important nuclei of the subcortical auditory system include two cochlear (CNc), ventral (VCNc) and dorsal (DCNc) nuclei, the nucleus of the midbrain inferior colliculi (ICNc) and the nucleus of the medial geniculate body (MGBNc). There are several sources of blood supply for these structures.

Lateral branches of the anterior inferior cerebellar artery (AICA) supply DCNc and VCNc, as well as adjacent parts of the vestibular complex [1], while in a small percentage both cochlear nuclei are vascularized by the posterior inferior cerebellar artery (PICA) [2]. Duvernoy [3], due to their vascularization, placed cochlear nuclei outside the three vascular zones of the medulla oblongata. The results of his research show that the vascular network of the DCNc is not particularly dense in humans and that it is nourished by small blood vessels, while the VCNc is slightly less vascularized than the dorsal one.

ICNc is an important relay nucleus of the auditory system, which integrates information about the frequency and the location of the sound [4]. It is located within the inferior colliculi, which are localized below the tentorial tip in the quadrigeminal cistern on the posterior surface of the midbrain [5]. The rostral tree of the superior cerebellar artery (SCA) and its long circumflex branches vascularize the inferior colliculi [1, 5]. ICNc is also supplied by collicular artery branches, from the posterior cerebral artery (PCA). This network is especially developed in the area of the rostral parts and on the peripheral edge of the inferior colliculi. Some vessels of this network also supply the intercollicular commissure [1]. The inferior colliculus is considered as one of the most densely vascularized regions of the brainstem [3].

MGBNc plays a central role in the auditory process. It transmits auditory information for higher-order processing to the primary auditory cortex, however, a reciprocal link from the primary auditory cortex back to MGBNc is also important [6, 7]. MGBNc is supplied by several sources: thalamogeniculate artery, posterior medial choroidal artery, mesencephalothalamic artery and branches of the calcarine artery, which originates from PCA [1]. P2 segment of the PCA provides several lateral branches, including five to ten inferolateral branches (thalamogeniculate arteries), which supply inferolateral thalamic territory. They enter the thalamus after passing between the MGB and LGB, where they give the medial and inferolateral pulvinar branches. Medial branches supply MGB [1, 8, 9]. PCA branch, posterior choroidal artery, arises either from the distal part of the P1 or proximal part of the P2 segment of PCA and supplies the posterior thalamic territory [10]. Its medial branches pass below the corpus callosum to the choroid plexus, while the lateral branches reach the cerebral crus, thalamus, and choroid plexus. The vascular territory of this artery, besides the pulvinar and intralaminar region, are both geniculate bodies [1, 8, 11]. Some branches for MGB also arise from mesencephalothalamic artery, long circumflex artery, and calcarine artery (PCA branches) [1].

The aim of this study was to perform a stereological analysis of the vascular network of subcortical auditory centers and to determine: volume, surface, and length density of the vascular network of the mentioned structures, and to determine whether there are differences in these parameters among examined structures.

Methods

The study was performed with the permission of the Ethics Committee of the University Clinical Center of Republic of Srpska, Banja Luka, Bosnia and Herzegovina, on samples of 12 brains of adults of both sexes, aged 31 to 75 years (average age 57.07 years), who died without diagnosed neurological diseases. With the usual autopsy technique, the brains were removed from the cranial cavity and then immersion-fixed in 10% formalin. After fixation, the brainstems were separated by cutting the brain masses at the level of the posterior edge of the mammillary bodies of the hypothalamus and from the cerebellum, by cutting the cerebellar pedicles. The brain stems were then cut into three strata in the transverse plane (5 mm thick: stratified sampling). The caudal stratum for analyses of CNc was formed by cutting the brainstem at the junction of the middle and rostral thirds of the olivar bulge and 5 mm rostrally, and the rostral stratum, which contains ICNc, was taken from the midbrain tissue from the caudal to the rostral border of the ICN. By cutting the corpus callosum and the structures of the midbrain, we separated the right from the left hemisphere of the brain. With a frontal section at the level of the pulvinar thalami, MGB, and LGB, and a cross-section of 5 mm rostrally, we formed the third stratum, representing the sample for analyzing MGBNc parameters [12]. The resulting strata were molded into paraffin blocks and cut in the transverse plane

Mallory method. From each section, images of visual fields were taken using a Leica EC3 camera (Leica Microsystems CMS GmbH, Wetzlar, Germany), TIFF format, resolution 2048 x 1536 pixels, at magnification x400 of the light microscope Leica DM 1000 (Leica Microsystems CMS GmbH, Wetzlar, Germany) and x0.7 magnification of the c-mount of camera. During sampling, visual fields were randomly selected. The number of visual fields was determined according to De Hoff's formula:

into 4µm thick sections and stained with the

$$n = (200 / y \bullet s / x)2$$

n - number of fields to be analyzed; x - mean of the orientation sample; s - standard deviation of the orientation sample; y - allowed deviation of the results from the arithmetic mean

ImageJ, version 1.53a (National Institutes of Health, Bethesda, USA) was used for stereological analysis. After spatial calibration with an object micrometer, the parameters of the test system A 100 were determined, based on which, using grid option in ImageJ, a network test system A 100 was formed (Table 1).

$$Lt = Pt \cdot d \cdot 2$$
 $At = Pt \cdot d2$

Subcortical auditory centers

Test system parameter	Value under x400 magnification
Pt	100
d	0.020386 mm
Lt	4.0772 mm
At	0.04156 mm2

Table 1. Basic parameters of the test system A 100

Pt - number of points in the test system; d - length of one line of the test system; Lt - length of all test lines; At - surface of the test area

All images were analyzed with the cell counter tool. The following stereological parameters of the vascular network of subcortical auditory centers were determined:

The volume density (Vv) was calculated using the formula: Vv (mm0) = Pf / Pt (Pf number of hits of test points falling on the studied phase; Pt - total number of points within the reference A-100 system [13].

Surface density (Sv) was determined based on the formula: Sv (mm-1) = $2 \cdot If / Lt$ (If – the number of cross-sections of the test phase with test lines; Lt - total length of test lines) [14].

Length density (Lv) was calculated according to the formula: Lv = 2xQf / At (mm-2), where Qf is the number of punctures of the examined structure in the test area, At - the surface of the test area [13].

The number of examined test fields (total research sample) for each variable is shown in the table 2.

Table 2. Number of analyzed test fields for each tested variable

Daramatar	Number o	Number of analyzed test fields				
I didilletei	CNc	ICNc	MGBNc			
Vv	1308	734	507			
Sv	792	767	389			
Lv	570	636	365			

Vv - volume density; Sv - surface density; Lv - length density; CNc - cochlear nuclei; ICNc - inferior colliculus nucleus; MGBNc - medial geniculate body nucleus Statistical analysis was performed with SPSS software, version 16.0, using descriptive statistics methods and Student's t-test. The value of p< 0.05 was considered statistically significant.

Results

The mean value of Vv was highest in MGBNc and lowest in ICNc (Table 3).

Statistical analysis using Student's t-test showed that there was no statistically significant difference (p = 0.548) in the Vv of the vascular network CNc and ICNc, but that there was a highly statistically significant difference between CNc and MGBNc (p<0.001) as well as between Vv of the vascular network of ICNc and MGBNc (p<0.001).

Table 3. Average values of Vv of the vascularnetwork of the examined structures

Structure	Vv (mm0) ± SD
CNc	0.02650 ± 0.00295
ICNc	0.02587 ± 0.00196
MGBNc	0.03386 ± 0.00183

CNc - cochlear nuclei; ICNc - inferior colliculus nucleus; MGBNc - medial geniculate body nucleus

When it comes to the Sv of the vascular network of subcortical auditory centers, the highest values were also seen in MGBN (Table 4).

Similar to Vv, comparison of values of Sv showed no statistically significant difference (p=0.398) between CNc and ICNc, but that there was a highly statistically significant difference between CNc and MGBNc (p<0.001) as well as between ICNc and MGBNc (p<0.001).

The third parameter (Lv) increased from the caudal to the rostral subcortical auditory center (Table 5).

There was a highly statistical difference (p<0.001) in the Lv of the vascular networks between all three examined structures.

Table 4. Values of the average Sv of the vascularnetwork of the examined structures

Structure	Sv (mm-1) ± SD
CNc	8.0037 ± 0.111998
ICNc	7.8325 ± 0.622
MGBNc	12.4815 ± 1.0358

CNc - cochlear nuclei; ICNc - inferior colliculus nucleus; MGBNc - medial geniculate body nucleus

Table 5. Values of Lv of subcortical auditory center

CNc - cochlear nuclei; ICNc - inferior colliculus nucleus; MGBNc - medial geniculate body nucleus

Discussion

There is a wide distribution of changes in the blood vessels of the brain, which are not only a consequence of degenerative changes caused by age, but also of the modern way of life, and numerous predisposing factors. Although they have the same sources of vascularization and topographic position, the symptoms of the auditory system in cases of cerebral ischemia are much rarer than the vestibular symptoms. Hearing loss often becomes clinically evident only after successive bilateral infarctions occur. Tinnitus is probably the most common auditory symptom, reported spontaneously by patients with stroke [15]. Hearing loss or tinnitus may be the first symptom of a stroke or occur with latency for up to a few days. They are most often the result of a stroke in the territory of AICA [16, 17], which leads to acute loss of audiovestibular function, affecting other structures in the vascular field of AICA - the facial and abducens nucleus, pyramid tract, and sensitive pathways [18, 19].

In cases of lateral lower pons syndrome, symptoms such as deafness and tinnitus also occur, due to the involvement of the auditory nerve or its nuclei [20]. Although ICNc belongs to the vascular field of SCA, there are rare cases of hearing problems after a stroke in the field of this blood vessel. Similarly, ischemia in the PCA field may involve inferior brachium or MGBNc, but auditory symptoms have not been reported [15, 21].

The results of this study show that there is no statistically significant difference in the volume and surface densities of the vascular network CNc and ICNc, but there is a difference in length density. All three stereological parameters of MGBNc were larger than the same parameters of CNc and ICNc, and the difference was highly statistically significant. This indicates the difference in the density and diameter of the blood vessels of these structures. MGBNc has a significantly larger vascular network than two other examined structures. Therefore, the volume of the MGB-Nc vascular bed is higher due to the diameter of the blood vessels. Also, blood vessels are more tortuous in ICNc compared to CNc, but even more in MGBNc. Larger diameter and more tortuous blood vessels predispose MGBNc to a slower blood flow, and therefore greater susceptibility to vascular incidents.

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Häusler and Levine [15] explain that significantly lower manifestation of auditory symptoms, compared to vestibular in cases of ischemia, is caused by a lower spreading of the auditory pathway, which makes the probability of ischemia affecting the auditory pathway on this basis lower. Also, a contributing factor is that parts of the auditory pathway, such as ICNc and MGBNc, have multiple sources of blood supply, with the vascular bed of MGB alone being significantly larger, indicating the absence of symptoms during changes in individual blood vessels [21]. The third factor is the abundance of the central auditory system and its strong representation above the level of the cochlear nuclei [15]. Therefore, rostral of cochlear nuclei, severe hearing deficits occur only if the damage is bilateral, and patients with widespread bilateral impairments of the auditory system are unable to respond or the disorder is incompatible with life.

Conclusion

The CNc and ICNc are supplied by vessels of similar density and diameter, but vessels in ICNc are more tortous. Blood vessels in MGB-Nc are significantly larger and more tortous than vessels in CNc and ICNc.

consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Stereološka analiza vaskularne mreže subkortikalnih auditivnih centara

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Uvod. Subkortikalni auditivni centri imaju nekoliko izvora vaskularizacije. Kohlearna jedra vaskularizuju grane a. cerebelli anterior inferior. A. cerebelli superior i a. cerebri posterior vaskularizuju jedro donjih kolikula, dok jedro unutrašnjeg koljenastog tijela vaskularizuje nekoliko grana a. cerebri posterior. Cilj istraživanja je kvantifikacija vaskularne mreže subkortikalnih auditivnih centara.

Metode. Dvanaest mozgova odraslih osoba, oba pola, životne dobi od 21 do 78 godina, bez znakova neuroloških oboljenja analizirano je u ovoj studiji. Uzorci za histološke preparate, bojeni su Mallory metodom, dobijeni su iz stratuma rezanih u nivoima: spoja srednje i rostralne trećine olivarnog ispupčenja, donjih kvržica srednjeg mozga i pulvinar-a thalami. Analizirani su stereološki parametri: volumenska, površinska i dužinska gustina vaskularne mreže subkortikalnih auditivnih centara.

Rezultati. Svi ispitivani stereološki parametri su imali najveće vrijednosti kod jedra unutrašnjeg koljenastog tijela. Statistički značajna razlika postojala je u volumenskoj, površinskoj i dužinskoj gustini između vaskularnih mreža kohlearnog jedra i jedra medijalnog koljenastog tijela, kao i između jedra donjih kolikula i jedra unutrašnjeg koljenastog tijela. Krvni sudovi kohlearnog jedra i jedra donjih kolikula su se razlikovali samo u dužinskoj gustini.

Zaključak. Krvni sudovi kohlearnog jedra i jedra donjih kolikula imaju sličnu gustinu i prečnik, ali su sudovi jedra donjih kolikula tortuozniji. U jedru unutrašnjeg koljenastog tijela krvni sudovi su veći, gušći i tortuozniji u odnosu na ostala dva subkortikalna auditivna centra.

Ključne riječi: kohlearna jedra, donji kolikuli, medijalno koljenasto tijelo, krvni sudovi



Original article

Analysis of CD31 expression and vascular parameters in human placentas from pregnant women with intrauterine growth restriction

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Summary

Introduction. Placental dysfunction is underlying cause in most of the intrauterine growth restriction and the pregnancy complications where the fetus does not achieve its genetically determined potential for growth. The critical process for the development of the placenta is angiogenesis. CD31 is an important endothelial adhesion protein that enables angiogenesis. The study aimed to analyze the CD31 expression and vascular parameters in normal placentas and IUGR placentas.

Methods. Thirty placental samples, fifteen IUGR placentas, and fifteen term normal placental samples were analyzed. The hematoxylin-eosin method and immunohistochemical method with anti CD31 antibody were used for the staining of the tissue sections. The analyzed vascular parameters were: capillary number density (CND), capillary area density (CAD), and capillary surface density (CSD).

Results. Between normal placentas and IUGR placentas there was no determined difference in CD31 expression. Positive intensive staining of CD31 was found in the endothelium of all blood vessels and no staining was observed in cytotrophoblast and syncytiotrophoblast cells. In IUGR placentas, CND of 2.55 capillary/1000 μ m2 villous area was significantly decreased compared to normal placentas of 3.49 capillary/1000 μ m2 villous area. CAD in IUGR placentas of 30.49 % was significantly decreased compared to normal placentas of 52.80 % villous area. CSD in IUGR placentas (92.81 μ m/1000 μ m2) was significantly reduced compared to CSD in normal placentas (145.51 μ m/1000 μ m2).

Conclusion. The localization and intensity of CD31 expression were not different between the IUGR and normal placentas. Histological vascular parameters of placental villi are decreased in the IUGR placenta. In case of intrauterine growth restriction, there is a reduced vascularization of the terminal villi of the placenta.

Keywords: placenta, intrauterine growth restriction, CD31 expression, vasculature

Introduction

The placenta is an organ that provides nutrients and oxygen for fetal development. Placental dysfunction is underlying cause in most of the intrauterine growth restriction, IUGR [1, 2]. Fetal growth restriction (FGR) is the complication of pregnancy where the fetus does not achieve its potential for growth that is determined genetically. IUGR occurs in 5-10% of all pregnancies. Increased perinatal morbidity and mortality are associated with IUGR. Also, serious health consequences in childhood and later in adulthood are associated with IUGR, including an increased risk for hypertension, cardiovascular diseases, obesity, diabetes mellitus type 2, and dyslipidemia [3, 4]. Various fetal and maternal factors may cause IUGR, but underlying insufficiency of the placenta is associated with the majority of the IUGR. It is believed that poor vascular development is associated with IUGR. Angiogenesis is a placental factor playing an important role [5, 6]. It is a critical process for the development of the placenta, as well as for all tissues [7-10]. The capillary network is formed with angiogenesis in which branching, sprouting, and lateral outgrowth of new vessels from pre-existing tubes occur. Different changes occur during this process, including increased endothelial cell proliferation, migration, the formation of endothelial cell tubes, increased vascular permeability, and finally, the coating of the outer surface of the capillary by pericytes and the formation of a stable vessel. CD31 is a transmembrane protein and is a member of the immunoglobulin family. It is an important endothelial adhesion protein that enables endothelial integrity and angiogenesis [11-13]. CD31 participates in the migration of endothelial cells and consequently the formation of new vascular vessels. It is a junctional protein containing an extracellular domain, a transmembrane domain, and a cytoplasmic domain (exons 9-16). The cytoplasmic domain is functionally

the most important domain that can undergo alternative splicing and result in different isoforms. The mechanism by which CD31 enables cell migration appears to be due to altering the cytoskeleton. Antibodies against CD31 inhibit the capability of the endothelial cells for the formation of the tube-like structures which are the initial form of new blood vessels. In IUGR placentas hypoxic damages have been recorded and analyses of vascular growth are necessary.

In studies that have investigated the placental vasculature in IUGR, histological abnormalities in chorionic arteries have not been found, but in the stem villous arteries obliteration of vessels lumen and hypertrophy have been found [14]. The reports on the vascularity of the terminal villus varied. In the part near the placental center, a significant difference in microvascularity was not observed between the IUGR placenta and the normal term placenta. The results of previous studies indicate the presence of decreased placental vascularisation in the periphery of IUGR placentas [14, 15]. The study has aimed to investigate the expression of CD31 and the vascular parameters in the placentas of pregnant women with uncomplicated term pregnancies and placentas of pregnant women with IUGR.

Methods

The study analyzed thirty placental samples, fifteen IUGR placentas, and fifteen normal term placental samples (from the 38th to the 40th week of gestation) of healthy pregnant women. The obtained placentas were without visible macroscopic changes and damage. From all placentas, one tissue sample size 1×1 cm was taken at a medium distance from the center and margin of the placenta. The samples represent whole-thickness placental pieces from basal to chorionic plates. Tissue sections 5 µm thick were made. The standard hematoxylin-eosin method and immunohistochemical staining method

with anti CD31 antibody (Dako) were used for staining of tissue sections. Antibody unmasking was performed for 20 min in citrate buffer at pH 6.0. Thereafter, tissue sections were incubated with a 3% hydrogen peroxide solution for 10 minutes at room temperature to block endogenous peroxidase activity [16]. Phosphate buffer (Dako, EnVsion FLEX WASH BUFER) was used to wash the tissue section three times for two minutes. UV block for five minutes to block nonspecific background staining was used. Incubation with primary antibody (monoclonal ab-CD31, clone JC / 70A 1:100) was performed for 30 minutes at room temperature. At room temperature, the incubation with the primary antibody (monoclonal ab-CD31, clone JC / 70A 1: 100) for 30 minutes was performed. The UltraVision LP Detection System (Thermo Scientific) was used for visualization. After washing with wash buffer three times for three minutes, DAB chromogen was used and the reaction was monitored under a microscope. Mayer hematoxylin was used as a counterstain.

The obtained samples were photographed using a Leica DM 6000 microscope. Vascularization was analyzed on microphotographs made at x200 magnification by using Image Analysis LAS V4.3 software. The following parameters were analyzed on CD31 positive capillaries within the terminal villi: capillary number density (CND) as a total number of capillaries per tissue area unit, capillary area densities (CAD) as the total area of the capillary as a proportion of total tissue area, and capillary surface density (CSD) as the total circumference of the capillary per tissue area unit, as previously described by Borowicz P. et al. [6]. The obtained data were statistically analyzed with Levene's test and t-test, using a licensed version of SPSS software 19.0.

Results

Normal placentas were obtained from fifteen women with an uncomplicated pregnancy

who delivered in term and whose life age was 32.51 ± 6.07 years. The life age of pregnant women with IUGR was 32.36 ± 5.95 years (Table 1). The mean gestational age at delivery of non-IUGR pregnancies was 38.49 ± 0,55 weeks and the mean gestational age of pregnant women with IUGR was 35.04 ± 3.11 weeks. In pregnant women with IUGR, the following were present: pregnancy-induced hypertension (PIH) in two pregnant women (13.33%), anemia in three pregnant women (20.00%), Rh incompatibility in two pregnant women (13.33%), coagulation disorder (thrombophilia) in two pregnant women (13.33%), hypothyreosis in three pregnant women (20.00%), bronchial asthma in one pregnant woman (6.67%), smoking in two pregnant women (13.33%), uterine anomaly (septum uteri, or uterus bicornis) in two pregnant women (13.33%), oligohydramnios in three pregnant women (20.00%), umbilical cord around the neck of the fetus (funiculus umbilicalis circum colli - FUCC) in three pregnant women (20.00 %). Some pregnant women had two or more of the listed risk factors.

Histological analysis of IUGR placentas showed increased syncytial knots, the sparser arrangement of terminal villi, and reduced vascular structures compared to normal placentas (Figure 1).

In all analyzed placentas the blood vessels of the chorionic plate and stem villi were overlaid with CD31 positive endothelium. Also, the endothelium of blood vessels of the intermediate villi and the capillaries in the terminal villi were CD31 positive. Cytotrophoblast cells and syncytiotrophoblast cells in all analyzed placentas were not positive for CD31 (Figure 2). There was no difference in the intensity and localization of CD31 expression between normal placentas and IUGR placentas (Figure 2).

Vascular density was analyzed in normal placentas and IUGR placentas (Table 1).

In normal placentas CND of 3.49 ± 1.39 capillary/1000 µm2 villous area was determined. The lowest determined value was 1,44 capil-



Figure 1. Placental villi: A. Normal term placenta, B. IUGR placenta (HE, x200)



Figure 2. C D 31 positive endothelium in villi vessels A. Normal term placenta, B. IUGR placenta (anti-CD31, x200)

		Placentas of the normal pregnanciesPlacentas of the pregr complicated by IU		he pregnancies ed by IUGR	
	Number	М	SD	М	SD
Life age (years)	15	32.51	6.07	32.36	5.95
Placentas of the pregnancies complicated by IUGR (gestational weeks)	15	38.49	0.55	35.04	3.11

Table 1. Life age and gestational age at birth of pregnant women whose placenta was analyzed

M - mean value, SD - standard deviation

lary/1000 μ m2, and the highest value was 5.31 capillary/1000 μ m2. In IUGR placentas CND of 2.55 \pm 0.55 capillary/1000 μ m2 villous area was determined. The lowest determined value was 1.26 capillary/1000 μ m2, and the highest value

was 3.20 capillary/1000 μ m2. Compared to normal placentas, in IUGR placentas a statistically significant decrease in CND with the use of Levene's test for equality of variances was determined (t = 2.459, df = 17.95, p = 0.024).

	CND (capillary/1000 µm2 villous area)			CAD (%)			CSD (µm/1000 µm2 villous area)			
	Ν	Min	Max	MV	Min	Max	MV	Min	Max	MV
Normal placentas	15	1.44	5.31	3.49	41.20	68.13	52.80	102.44	217.56	145.51
IUGR placentas	15	1.26	3.20	2.55	19.90	45.95	30.49	71.93	125.44	92.81

fable 2. Histological vascu	ar parameters in normal	term placentas and IUGR	placentas
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N - number of analyzed placentas, Min - the lowest value, Max - the highest value, M - mean value

CAD in normal placentas was 52.80 ± 7.91 %, and in IUGR placentas was 30.49 ± 6.54 % (Figure 3). In normal placentas, the lowest determined value was 41.20%, and the highest value was 68.13%. In IUGR placentas the lowest determined value was 19.90%, and the highest value was 45.95%. Between normal placentas and IUGR placentas a statistically significant difference with the use of the t-test was determined. CAD was significantly reduced in the IUGR placentas (t = 8.42, p = 0.0001).

CSD in normal placentas was 145.51 ± 31.39 µm/1000 µm2 villous area, and in IUGR placentas it was 92.81 ± 20.86 µm/1000 µm2 villous area. In normal placentas, the lowest determined CSD value was 102.44 µm/1000 µm2 villous area, and the highest CSD value was 217.56 µm/1000 µm2 villous area. In IUGR placentas the lowest determined CSD value was 71.93 µm/1000 µm2 villous area, and the highest CSD value was 71.93 µm/1000 µm2 villous area, and the highest CSD value was 125.44 µm/1000 µm2 villous area. Compared to normal placentas CSD in IUGR placentas was significantly reduced (t=5.415, df=28, p=.000).

Discussion

The important cause of perinatal morbidity and mortality is IUGR. The IUGR will occur in 5–10% of all pregnancies, while in countries with low income the incidence is 15–20%. IUGR is present in 26% of stillbirths and influences adult health in long term [2–5]. Because of that, it is important to diagnose IUGR accurately and on time and to properly manage pregnancy complicated with IUGR.

Intrauterine fetal growth can be impaired by fetal, placental, maternal, and environmental factors. Considering the time of diagnosis and Doppler ultrasound parameters, IUGR is divided into early-onset IUGR and late-onset IUGR. Early IUGR accounts for 20-30% of all IUGR and is associated with preeclampsia in 50% of cases. Late-onset IUGR accounts for 70-80% of all IUGR and is associated with preeclampsia in 10% of cases. The placenta plays an important role because insufficient placental function leads to abnormal fetal growth. In the background of placental insufficiency is the abnormal development of the placenta. In IUGR placentas there are histological changes including syncytial knots, the sparse arrangement of terminal villi, and reduced vascular structures. Histological changes in IUGR placentas, which are hypoxic lesions that occurred by reducing utero-placental or feto-placental flow, were determined in previous studies: widespread infarct areas, increased syncytial knots, the absent or reduced lumen of the blood vessel, vascular thrombosis, villous hypoplasia [1,15,17].

The placental factor that could be the cause of the development of IUGR is inadequate angiogenesis in the placenta and decreased maternal-fetal blood flow [1,15]. In this study, positive intensive staining of CD31 was found in endothelial cells of all placental blood vessels and no staining was observed in cytotrophoblast and syncytiotrophoblast cells. There was no difference in the intensity and the type of cells positive for CD31 expression between normal placentas and IUGR placentas. In literature, the study that analyzed the expression of CD31 in IUGR placentas by immunohistochemistry found no differences between normal and IUGR placentas [10]. CD31 is an important endothelial adhesion protein that mediates angiogenesis. It is the main endothelial marker for the analysis of vascular growth. Due to the fact that hypoxic damage has been recorded in IUGR placentas, analyses of vascular growth in the placenta are necessary. This endothelial marker was used to analyze placental microcirculation in IUGR placentas.

The present study showed the hypovascularity of terminal villi at a medium distance between the center and the periphery of the IUGR placenta. CND (the parameter that indicates the number of capillaries in the villi), CAD (the parameter that indicates the size of the villous part built by the capillaries), and CSD (the parameter that indicates the size of the circumference of villous capillaries), were reduced in IUGR placentas. CND in IUGR placentas (2.55 ± 0.55 capillary/1000 µm2villous area) was significantly reduced compared to normal placentas (3.49 ± 1.39 capillary/1000 µm2 villous area). Also, CAD and CSD in IUGR placentas (30.49 ± 6.54 %; 92.81 ± 20.86 μm/1000 μm2 villous area) were significantly reduced compared to normal placentas (52.80 ± 7.91 %; 145.51 ± 31.39 μm/1000 μm2 villous area).

In a normal placenta, Aughwane et. al analyzed vascular density in relation to the location from cord insertion to the placental edge. On histological analysis, a difference in villous vascular density with distance from the umbilical cord insertion was not determined [18]. Between birthweight and placental vascular malperfusion lesions, and also adverse neonatal outcome, there was a negative correlation [19]. The analysis of the macrovasculature in normal and FGR placentas, with the use of computed tomography angiography revealed no difference between normal and IUGR placentas [20].

In preeclamptic placentas, Li et. al directly counted and measured the CD31 stained capillaries with the use of digital image analysis that might estimate more precisely vascular changes in the placenta. They found no difference in CND between normal placentas (the medium value of 2.77 capillary/1000 μ m2 villous area) and severe preeclamptic placentas (the medium value was 2.83 capillary/1000 μ m2 villous area) [9].

In literature data about villous vascularity of IUGR placentas was determined with stereology measurements and they alter significantly in the different areas of IUGR placentas. In the area near the center of the placenta, between IUGR and normal placentas was no significant difference in vascularity. Significantly reduced vascularity of the villi was determined at the periphery of IUGR placentas [14]. In this study vascularity of terminal villi was analyzed at the medium distance between insertion of the umbilical cord and placental margin. At medium distance vascularity of terminal villi was reduced.

The results obtained in this study support the findings of altered angiogenesis and reduced vascularization of the terminal villi in the placentas from pregnancy with intrauterine growth restriction of the fetus.

Conclusion

The localization and intensity of CD31 expression in the IUGR placenta are not different compared to the normal placenta. Histological vascular parameters of placental villi are decreased in the IUGR placenta. In the intrauterine growth restriction decreased vascularity of terminal villi of the placenta is present. **Funding source.** The authors received no specific funding for this work.

Ethical approval. The Ethics Committee of the University Clinical Center of Republic Srpska in Banja Luka approved the study and informed consent was obtained

from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Analiza ekspresije CD31 i vaskularnih parametara u humanim posteljicama od trudnica sa intrauterinim zastojem rasta

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Uvod. Disfunkcija posteljice se nalazi u osnovi većine intrauterinih zastoja rasta ploda, komplikacije trudnoće u kojoj fetus ne postiže svoj genetski određen potencijal za rast. Proces koji je kritičan za razvoj posteljice je angiogeneza. Cilj studije je bio da se analiziraju ekspresija CD31 i vaskularni parametri u normalnoj posteljici i posteljici kod intrauterinog zastoja rasta (intrauterine growth restriction - IUGR).

Metode. Trideset uzoraka posteljica, petnaest posteljica kod IUGR i petnaest uzoraka normalne terminske posteljice je analizirano. Hematoksilin-eozin metoda i imunohistohemijska metoda sa antiCD31 antitijelom su korišćene za bojenje tkivnih rezova. Analizirani su vaskularni parametri: numerička gustina kapilara (cappilary number density - CND), arealna gustina kapilara (capillary area density - CAD) i površinska gustina kapilara (capillary surface density - CSD).

Rezultati. Između normalnih posteljica i posteljica sa IUGR nije utvrđena razlika u CD31 ekspresiji. Intenzivno pozitivno CD31 bojenje je nađeno u endotelu svih krvnih sudova i nije uočeno pozitivno bojenje u citotrofoblastu i sinciciotrofoblastu. CND u IUGR posteljicama od 2,55 kapilara/1000 µm2 površine resice je značajno smanjen u poređenju sa normalnim posteljicama od 3,49 kapilara/1000 µm2. CAD u IUGR posteljicama od 30,49 % je značajno smanjen u poređenju sa normalnim posteljicama od 52,80 % površine resice. CSD u IUGR posteljicama (92,81 µm/1000µm2) je značajno smanjen u poređenju sa CSD u normalnim posteljicama (145,51 µm/1000µm2).

Zaključak. Lokalizacija i intenzitet ekspresije CD31 se nisu razlikovali između IUGR posteljice i normalne posteljice. Histološki vaskularni parametri resica posteljice su smanjeni u IUGR posteljici. Kod intrauterinog zastoja rasta ploda prisutna je smanjena vaskularizovanost terminalnih resica posteljice.

Ključne riječi: posteljica, intrauterini zastoj rasta, ekspresija CD31, vaskulatura



Original article

The use of personal protective equipment by the employees in COVID-19 Departments of the University Clinical Center of Republic of Srpska and the risk assessment of the new coronavirus

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Summary

Introduction. Assessment of the occupational risk of exposure to the new coronavirus of workers engaged in the COVID-19 Departments of the University Clinical Center of Republic of Srpska and the use of personal protective equipment was the aim of this research.

Method. In the University Clinical Center of Republic of Srpska (UKC RS), in the COVID-19 Departments, a KAP study (Knowledge Attitudes Practice Study) was conducted among 102 employees of all educational profiles, using the questionnaire of the World Health Organization (WHO), which was adapted for this research. The survey was voluntary and anonymous with the informed approval consent of the respondent.

Results. Out of 102 surveyed, 13 of them tested positive for SARS-CoV-2. On average, 95.0% of respondents always wear PPE in the COVID-19 Departments of the UKC RS. Putting on/removing PPE and decontamination of contact surfaces have been always carried out by 88.2% of respondents. Out of 64 respondents who used PPE for aero-sol generating procedures, 10 of them (15.6%) were positive for SARS-CoV-2 and of the other 38 respondents who did not participate in such procedures, three of them (7.9%) were positive for SARS-CoV-2. Statistical data processing was done in the SPSS program package, version 20.0, with a significance level of difference of 5% (p=0.412).

Conclusion. There was no significant difference between SARS-CoV-2 positive and negative personnel regarding the use and change of PPE, hand hygiene and surface decontamination. The assessment of the occupational risk of exposure to SARS-CoV-2, in addition to the proper use of PPE, takes into account the local epidemiological situation, specific characteristics of the work environment and tasks, the hierarchy of controls and the level of adherence to preventive measures and infection control.

Keywords: pandemic, new coronavirus, personal protective equipment

Introduction

In the COVID-19 pandemic, healthcare workers have a great burden and responsibility. COVID-19 is an infectious respiratory disease caused by a new coronavirus, called SARS-CoV-2, which is primarily spread by respiratory droplets, then secretions from the respiratory tract or by

direct contact. However, there is a possibility of transmission through the air when a person is exposed to a high concentration of aerosols in a relatively closed environment or during aerosol- generating medical procedures. In addition, SARS-CoV-2 RNA was detected in feces and urine, which requires special attention to the protection of the environment [1]. Employees must be educated on the use of PPE, hand hygiene, ward disinfection, medical waste management and sterilization of patient care equipment and occupational exposure management [2]. In order to ensure awareness and knowledge of protective infection control measures, it is necessary for hospitals to appoint and additionally educate a nurse/sanitary engineer on the use of PPE to train other healthcare workers on dressing, undressing and removing PPE [3].

Factors that contribute to the appearance of SARS-CoV-2 virus infection among healthcare workers are related to insufficient knowledge of the COVID-19 disease, inadequate use and availability of PPE, unavailability of diagnostic tests and psychological stress [4].

The results of the research on the number of healthcare workers infected with SARS-CoV-2, from most of the countries affected by the virus (Italy, China, America, Spain and France) have shown that the infection rate ranged from 15 to 18%, and in some cases up to 20% in this population. Healthcare workers are exposed to a greater risk of SARS-CoV-2 virus infection due to the nature of their work, which is also indicated by the data from the study by Nguyen et al. on the prevalence of COVID-19 in 2,747 cases per 100,000 who were infected at the workplace compared to 242 per 100,000 in the general community [5]. Inadequate knowledge and incorrect attitudes about COVID-19 disease among healthcare workers can directly influence practices and lead to delayed diagnosis, poor infection control and disease spread. In the study by Abdel Wahed et al, a positive correlation between grades, knowledge and attitudes was proven (r = 0.215, p< 0.001). About 83.1% of the study participants are afraid of being infected with the COVID-19, and the unavailability of PPE, fear of transmitting the disease to their families and social stigma were the most frequently reported reasons for increased risk perception [6]. However, due to direct exposure to COVID-19 patients, healthcare personnel must be educated on prevention and protection measures in order to be sufficiently capable of protecting themselves and others [7]. Medical workers should primarily observe preventive measures, such as the use of PPE, face masks (N95 or FFP2), eye protection (safety glasses, visors), coveralls and gloves, in order to prevent infection that is transmitted mainly through respiratory droplets or direct contact [8, 9].

At the beginning of the pandemic, in the UKC RS, many procedures were developed related to the prevention of the emergence and spread of the new corona-virus. Some of the first procedures are: "Measures to prevent and suppress the spread of the new coronavirus (SARS-CoV-2) in hospital conditions" describing "Instructions for the use of personal protective equipment (PPE)".

During the performance of therapeutic and diagnostic procedures where the formation of aerosols is expected, additional preventive measures for protection are necessary because of infectious agents that are transmitted through the air. In these cases, healthcare workers should take additional protection procedures using N95 masks or equivalents masks, face shields and eye protection glasses. These procedures include endotracheal intubation, non-invasive ventilation, tracheostomy, bronchoscopy, aspiration, cardiopulmonary resuscitation. Other technically high-risk nursing procedures are vein or artery puncture and collection of nasopharyngeal samples [10]. These procedures must be performed in well-ventilated rooms or negative pressure rooms, limiting the number of people present and leaving enough time for preparation, e.g. for emergency intubations.

In the UKC RS, high-risk procedures are performed according to prescribed procedures in negative pressure rooms, isolation rooms or single rooms that are well ventilated.

The aim of the research is to assess the risk of contracting coronavirus for the employees of the University Clinical Center of Republic of Srpska engaged in the COVID-19 departments in relation to their use of PPE.

Methods

In the COVID-19 Departments of the UKC RS, the KAP study was performed among employees of all education profiles using the World Health Organization questionnaire adapted for this research (World Health Organization: Risk assessment and management of exposure of health care workers in the context of COVID-19 Interim guidance, March 19, 2020).

Research included 102 respondents engaged in the COVID-19 Departments of the UKC RS from March 4, 2020 to March 3, 2021, and they voluntarily joined the research.

As a research instrument, an anonymous closed-type questionnaire was used for employees in the COVID-19 Departments, referring to the knowledge, attitudes and behavior towards COVID-19 preventive measures in UKC RS, risk assessments and actions in the event of exposure of health care workers to the virus, which causes COVID-19.

Employees in the COVID-19 Departments of the UKC RS who were present at work on the days of the research were surveyed and signed an informed consent to participate in the study. The sample consisted of employees involved in the treatment and provision of medical care to patients with the COVID-19 disease, those who were present in the same place as the patient and those who did not provide medical care but had contact with body fluids, potentially contaminated objects or surfaces. Therefore, the study included health professionals of all profiles (doctors, nurses, radiology technicians, laboratory technicians, physiotherapists), personnel in charge of hygiene maintenance, nutrition, patient transport, security, etc.

This questionnaire can also be used to determine non-compliance with recommendations. It can be used in all healthcare facilities where patients with the COVID-19 disease are placed. It is used for risk assessment and management after exposure of healthcare workers to the SARS-CoV-2 virus. Objectives of assessment of healthcare workers who are at risk of the COVID-19 infection are: to determine the categorization of each healthcare worker after exposure to a patient with the COVID-19 disease and based on the risk to implement measures to treat exposed healthcare workers.

The questionnaire contains 34 questions divided into four parts: the first part of eight questions includes questions about the sociodemographic characteristics of the respondents, the second part with 11 questions is related to adherence to recommendations for the prevention and control in healthcare services provided, the third part refers to questions related to adherence to recommendations for the infection prevention and control in aerosol generating procedures and this part has 13 questions, and the fourth part with two questions includes adverse events with biological material. In the survey, respondents responded to the offered answers, questions that were presented using a five-point Likert scale (1 - always as recommended, 2 - most of the time, 3 - occasionally, 4 - rarely, 5 - never) and with dichotomous answers: Yes or No.

Statistical analysis of the research results: the data for the respondents were entered into the Microsoft Office Excel database, which was created exclusively for the purposes of this research.

SPSS, version 20.0 (Statistical Product and Service Solutions), was used for statistical data processing. From the statistical methods of data processing, descriptive statistics were used, including the calculation of the standard deviation and mean value for continuous variables with a normal distribution and relative frequencies for categorical variables in order to get insight into the clinical course of the COVID-19 disease. For continuous variables, the significance of the difference was tested by parametric (Student's t-test) and non-parametric tests (Fisher's test) in case of irregular data distribution. For categorical variables, the chi-square test was used. Univariate and multivariate logistic regression was used to analyze the risk factors of infection caused by the SARS-CoV-2 virus among healthcare workers. The level of statistical significance is p < 0.05 for a 95% confidence interval. The research results are presented in tables and graphs. The research was conducted in accordance with all ethical principles.

Results

Total of 102 respondents, of all educational profiles, employees in the COVID-19 organizational Units (OU) of the UKC RS participated in the research. The largest number of respondents has a high school medical degree (60), followed by a graduate health care professional (16), a high school diploma (11), a basic education (10) and a University degree/ Doctor of Medicine (5). Most respondents (61) were engaged in patient care (nurses/technicians), followed by hygiene maintenance (17), supervisors/nurses (13), two respondents were infectious disease specialists, radiology engineers and auxiliary workers, and one respondent from three different specializations, a head nurse and a professional associate. Eighty three of them (81.37%) are female and 19 (18.62%) are male. All respondents, 102 (100%), declared that they used PPE in the COVID-19 organizational units (Table 1).

Table 1. Use of personal protective equipment in "COVID-19" organizational units

Use a PPE in COVID-19 organizational units					
	Employees in COVID-19 organizational units	Percentage	Valid percentage *	Cumulative percentage	
Yes	102	100.0	100.0	100.0	

Method of using individual PPE in "COVID-19" OJ; shows that out of 102 respondents, 95.0% of them declared that they used protective gloves-always as recommended, and a protective face mask was used by 99.0% of respondents always as recommended while only one respondent used it most of the time. Eye protection (visor/glasses) was used by 78.2% of respondents, always as recommended, 7.8% - most of the time and 13.2% - occasionally and rarely. A disposable suit/robe was used by 91.1% of respondents - always as recommended, 6.7% respondents - most of the time, and one examinee both occasionally and rarely (Figure 1).



Figure 1. Distribution of examinees' answers in regard to their use of individual PPE during the COVID19 epidemic

The method of changing/removing PPE and decontamination of contact surfaces indicates that 88.2% of 102 examinees change/remove PPE-always as recommended, 7.8% most of the time and 3.9% - change/remove PPE occasionally or rarely. That the contact surfaces were regularly or frequently decontaminated, always as recommended, was stated by 72.5% of respondents while 27.4% of them declared that they decontaminated contact surfaces most of the time, occasionally or rarely (Figure 2).



Figure 2. Distribution of examinees' answers in regard to the method of changing/removing PPE and decontamination of contact surfaces they practiced during the COVID19 epidemic

Table 2 shows the respondents answers linked for the use of personal protective equipment.

Of all respondents, who participated in aerosol generating procedures, 64 of them (62.7%) used personal protective equipment. The remaining 38 (36.3%) respondents did not participate in these procedures (Table 2).

Table 3 shows the use of PPE in relation to SARS-CoV-2 positive or negative personnel.

Out of 64 respondents, who used PPE in aerosol-generating procedures, 10 of them (15.6%) were positive for SARS-CoV-2, and 54 of them (84.4%) were negative for the SARS-CoV-2 virus. Out of 38 respondents, who did not participate in aerosol-generating procedures, three (7.9%) were positive for SAR-SCoV-2, and 35 (92.1%) were negative for this virus. Figure 3 shows the way to use individual PPE in aerosol generating procedures. Out of 64 respondents who participated in these procedures, 95.3% always had, as recommended, a protective N95/FFP2 face mask and 90.6% of the respondents wore a disposable protective suit/robe. Protective gloves, always, as recommended, were used by 93.7% and eye protection (visor/goggles) by 68.7%. Only 29.6% of respondents always used a waterproof apron in aerosol generating procedures as recommended, and 62.5% of respondents used it occasionally or never (Figure 3).

Use of PPE in procedures that generate an aerosol	Employees in COVID-19 organizational units	Percentage of respondents	Used PPE
Yes, everyone who used PPE in procedures that generate an aerosol	64	62.7	100.0
Unknown	1	1,0	
They have not participated in procedures in which aerosols are generated	37	36.3	
In total	102	100.0	100.0

Table 2. Use of PPE in procedures that generate an aerosol

* Valid percentage - refers to valid values/data

Use of PPE in relation to SARS-CoV-2 positive/negative personnel					
		SARS- positive/ne			
		Da	Ne	\sum	
	Number of staff	10	54	64	
Yes	% for the use of PPE	15.6%	84.4%	100.0%	
	% for staff positive for SARS-CoV-2	76.9%	60.7%	62.7%	
	Number of staff	3	35	38	
He/she did not participate	% for the use of PPE	7.9%	92.1%	100.0%	
in this procedure	% for staff positive for SARS-CoV-2	23.1%	39.3%	37.3%	
	Number of staff	13	89	102	
In total	% for the use of PPE	12.7%	87.3%	100.0%	
	% for staff positive for SARS-CoV-2	100.0%	100.0%	100.0%	

Table 3. Use of PPE in relation to SARS-CoV-2 positive/negative personnel



Figure 3. Distribution of examinees' answers in regard to using individual PPE in procedures in which aerosol is generated during the COVID19 epidemic

Table 4 shows the method of glove use in relation to SARS-CoV-2 positive or negative personnel in procedures in which aerosol is generated.

Out of 60 respondents who changed gloves - always as recommended, 10 (16.7%) were positive for SARS-CoV-2, and 50 (83.3%) were negative for this virus. Out of four respondents who changed gloves - most of the time, all was negative for SARSCoV-2. Out of 38 respondents who did not participate in aerosol-generating procedures, three (7.9%) respondents were positive for SARS-CoV-2, and the remaining 35 (92.1%) were negative for this virus (Table 4).

Glove use in relation to SARS-CoV-2 positive/negative personnel					
		SARS- positive/ne	CoV-2 gative staff		
		Yes	No	Σ	
	Number of staff	10	50	60	
Always as recommended	% for using gloves	16.7%	83.3%	100.0%	
	% for staff positive for SARS-CoV-2	76.9%	56.2%	58.8%	
Most of the time	Number of staff	0	4	4	
	% for using gloves	0.0%	100.0%	100.0%	
	% for staff positive for SARS-CoV-2	0.0%	4.5%	3.9%	
	Number of staff	3	35	38	
He/she did not participate	% for using gloves	7.9%	92.1%	100.0%	
in this procedure	% for staff positive for SARS-CoV-2	23.1%	39.3%	37.3%	
	Number of staff	13	89	102	
In total	% for using gloves	12.7%	87.3%	100.0%	
	% for staff positive for SARS-CoV-2	100.0%	100.0%	100.0%	

Table 4. Glove use in relation to SARS-CoV-2 positive/negative personnel

Table 5 shows the method of N95/FFP2 mask use in relation to SARS-CoV-2 positive or negative personnel in procedures where aerosol is generated.

Out of 61 respondents who used N95/ FFP2 masks - always as recommended, nine (14.8%) were positive for SARS-CoV-2 and 52 (85.2%) were negative for this virus. Out of three respondents who used N95/FFP2 masks - most of the time, one respondent (33.3%) was positive for SARS-CoV-2 and two (66.7%) were negative for this virus. Out of 38 respondents who did not participate in aerosol-generating procedures, three (7.9%) respondents were positive for SARS-CoV-2, and 35 (92.1%) were negative for this virus (Table 5).

Research related to the use of visors/goggles in relation to SARS-CoV-2 positive or negative personnel in aerosol-generating procedures indicates that out of 45 respondents who used visors/goggles - always as recommended, six of them (13.3%) were positive for SARS-CoV-2, and 39 (86.7%) were negative for this virus. Out of 12 respondents who used visors/goggles most of the time, two (16.7%) were positive for SARS-CoV-2 and 10 (83.3%) were negative for this virus. Out of seven respondents who used visors/ glasses - occasionally, two (28.6%) were positive for SARS-CoV-2, and 5 (71.4%) were negative for this virus. Of the 38 respondents who did not participate in aerosol-generating procedures, 3 (7.9%) were positive for SARS-CoV-2, and 35 (92.1%) were negative for this virus.

N95/FFP2 mask use in relation to SARS-CoV-2 positive/negative personnel					
		SARS-CoV-2 positive/negative staff			
		Yes	No	Σ	
Always as recommended	Number of staff	9	52	61	
	% to use the N95 mask	14.8%	85.2%	100.0%	
	% for staff positive for SARS-CoV-2	69.2%	58.4%	59.8%	
	Number of staff	1	2	3	
Most of the time	% to use the N95 mask	33.3%	66.7%	100.0%	
He/she did not participate in this procedure	% for staff positive for SARS-CoV-2	7.7%	2.2%	2.9%	
	Number of staff	3	35	38	
	% to use the N95 mask	7.9%	92.1%	100.0%	
	% for staff positive for SARS-CoV-2	23.1%	39.3%	37.3%	
In total	Number of staff	13	89	102	
	% to use the N95 mask	12.7%	87.3%	100.0%	
	% for staff positive for SARS-CoV-2	100.0%	100.0%	100.0%	

Table 5. N95/FFP2 mask use in relation to SARS-CoV-2	positive/negative personne
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The influence of the use of a protective suit/robe in relation to SARS-CoV-2 positive or negative personnel in aerosol generating procedures was examined where out of 58 respondents who used a protective suit/robe always as recommended, nine of them (15.5%) were positive for SARS-CoV-2, and 49 (84.5%) were negative for this virus. Out of five respondents who used a protective suit/robe most of the time, one respondent (20.0%) was positive for SARS-CoV-2 and 4 (80.0%) were tested negative for this virus. One respondent who used a protective suit/robe - occasionally tested negative for SARS-CoV-2. Out of 38 respondents who did not participate in aerosol-generating procedures, three (7.9%) respondents were positive for SARS-CoV-2, and 35 (92.1%) were negative for this virus.

The aerosol generating procedures was also examined. Out of 19 respondents who

used a waterproof apron - always as recommended - one (5.3%) was positive for SARS-CoV-2 and 18 (94.7%) were negative for this virus. Out of two respondents who used a waterproof apron - most of the time, both tested negative for this virus. Out of three respondents who occasionally used a waterproof apron, two (66.7%) were positive for SARS-CoV-2, and one (33.3%) was negative for this virus. Out of eight respondents who rarely used a waterproof apron, one (12.5%) was positive for SARS-CoV-2, and seven (87.5%) were negative for this virus. Out of 32 respondents who never used a waterproof apron, six (17.6%) were positive for SARS-CoV-2, and 26 (82.4%) were negative for this virus. Out of 38 respondents who did not participate in aerosol-generating procedures, three (7.9%) were positive for SARS-CoV-2, and 35 (92.1%) were negative for this virus.

Figure 4 shows the method of changing/ removing PPE and decontamination of contact surfaces in aerosol generating procedures.

Total of 96.0% respondents stated that they changed/removed PPE - always as recommended, and 9.3% of respondents most of the time or occasionally. That contact surfaces were regularly or frequently decontaminated - always as recommended was declared by 73.4% of respondents and 26.5% of respondents declared for most of the time, or occasionally. Thirty eight respondents did not participate in these procedures (Figure 4).



Figure 4. Distribution of examinees' answers in regard to method of changing/removing PPE and decontamination of contact surfaces in procedures in which aerosol is generated during the COVID19 epidemic

In aerosol generating procedures, 58 respondents participated in the research, in which the method of changing/removing PPE was examined in relation to SARS-CoV-2 positive or negative finding in the respondents. Among them, always as recommended, nine (15.5%) were positive for SARS-CoV-2, and 49 (84.5%) were negative for this virus. Of five respondents who changed/removed PPE, most of the time, one respondent (20.0%) was positive for SARS-CoV-2. while the others were negative. Respondents who did not participate in aerosol generating procedures, out of 38 of them, three (7.9%) were positive for SARS-CoV-2, and 35 (92.1%) were negative.

Out of 18 respondents who had adverse events with biological material, four (22.2%)

were positive for SARS-CoV-2, and 14 (77.8%) were negative for this virus. Out of 84 respondents who had no adverse events with biologicals material, nine (10.7%) of them were positive for SARS-CoV-2, and 75 (89.3%) were negative for this virus.

Discussion

Out of 102 surveyed, 13 (12.75%) were positive for SARS-CoV-2, and 89 (87.25%) were negative for this virus. Statistical analysis; for all variables (use of individual PPE, hand hygiene and surface decontamination) in relation to personnel positive or negative for SARS-CoV-2; t-calculated was compared with t-critical (obtained difference >0), the samples are statistically independent, and the difference is considered statistically significant (p = 0.412). It means that there is no significant difference between SARS-CoV-2 positive or negative personnel in relation to the use/change of PPE (gloves, mask, disposable coat, visor/ goggles, apron) and hand hygiene and surface decontamination. Prevalence studies of COVID-19 conducted in Italy, the Netherlands and the United Kingdom reported that the prevalence rate of COVID-19 among healthcare workers was 3%, 9% and 18% (238-240) [11, 12, 13]. Such study in the UKC RS was not performed while the results of the KAP study on the use of PPE and the assessment of the risk of COVID-19 among those surveyed indicate that 13.2% were positive for SARS-CoV-2. A cross-sectional study assessing the occupational risk of exposure to COVID-19 among healthcare workers was conducted from May to August 2020 in Ethiopia, Amhara Region. A total of 418 healthcare professionals including doctors, pharmacists, nurses, health officers, laboratory technicians and workers transporting patients participated in the study. Most respondents, 74.2%, were male, and 39% were nurses/midwives. More than a half of the respondents, actually 56.7%, stated that they had no face-to-face contact with the confirmed COVID-19 patient. Among respondents, 41.4%, 147 (35.2%), 63 (15.1%) and 65 (15.6%) of healthcare workers always used gloves, medical masks, face shield or glasses/safety glasses, and a disposable robe. In this study, persons aged 25–44 years, work experience of 21–30 years and good hand hygiene practices were protective factors against COVID-19. On the other hand, the perception of not being exposed to COVID-19 and the bad habit of decontamination of contact surfaces were risk factors associated with confirmed cases of COVID-19 among healthcare workers [14].

Healthcare workers are exposed to a big risk in the fight against COVID-19. Many healthcare workers were infected and died from COVID-19, and many of them were quarantined to prevent the spread of the infection [15]. COVID-19 is a greater risk for healthcare workers in the ICU, Emergency Department, Infectious Disease Department, Pulmonary Disease Department and other high-risk departments. Hand hygiene, proper hand washing and personal protective equipment are key to reducing the spread of the coronavirus in healthcare facilities and communities. Adequate training and resources are needed for healthcare workers to prevent cross-contamination to other patients treated in healthcare facilities [16–18]. It is important that hospitals have appropriate infection control procedures and sufficient PPE and disinfectants for personnel directly involved in the care of patients with COVID-19. In the UKC RS, since the beginning of the pandemic, continuous education has been provided to all employees on the prevention of intrahospital infections, proper use of PPE, medical waste management and occupational health and safety.

In the study in Ethiopia, the average age of the respondents was 33 and statistically there was a significant difference between the different age groups. Healthcare workers aged 25 to 34 were 80 times less likely to be infected with the COVID-19 infection than those aged 18 to 24. Also, healthcare workers aged 35 to 44 were 87 times less likely to infect with a COVID-19 infection than respondents aged 18–24. A study conducted on healthcare workers in the USA revealed that the average age of healthcare workers infected with COVID-19 was 42 [19]. A similar study conducted in China showed that the average age of infected healthcare workers was 37 [20].

According to a study conducted in Bangladesh, healthcare workers were contracting the COVID-19 infection at a fairly young age. However, in China, relatively older health professionals were affected by this infection, and the age variation among the healthcare workers was significant [16]. The results of a study conducted in China showed that the probability of infecting with COVID-19 was higher among healthcare workers working in the Emergency Department, although the difference was not statistically significant, while a study conducted in Bangladesh showed that the possibility of infecting with COVID-19 was higher among healthcare workers working in Intensive Care Units (ICU), also, the difference was not statistically significant [21].

A similar study conducted in Wuhan, China found that health care workers in the ICU were twice as likely as to infect with COVID-19 than those working in general departments [22]. This difference may be due to a change in the workplace, for which healthcare workers are not specialized in one department but are rotated due to a lack of personnel. Strategies should be implemented to establish effective and sustainable infection control measures that protect healthcare workers from COVID-19 infections through psychological support, incentives, availability of personal protective equipment, education/training, and personnel readiness [22]. The COVID-19 pandemic required quick action in all segments of society but the healthcare system has the biggest burden. There are still a lot of unknown things about this disease and all should still be in alert. Preventive measures are the only ones

that can stop the spread of a new viral infectious disease. Nurses, along with other healthcare professionals, are actively involved in interventions for managing the COVID-19 and represent the one of the key factors in stopping the pandemic. From the beginning, they have been actively involved in interventions for managing the COVID-19 and represent one of the key factors in stopping the pandemic. Since the beginning of the pandemic, caused by the new corona-virus, healthcare workers have been on the frontline of defense and many of them are already at the edge of endurance, both physically and mentally, and it is necessary for them to ensure a healthy working environment in order to strengthen their efforts to fight against COVID-19, to put under control this virus. Occupational health and safety is crucial for healthcare workers and associates of all educational profiles facing dangers of infections every day. It is important that hospitals have appropriate infection control procedures and sufficient PPE and disinfectants for personnel who are directly involved in the care of patients with the COVID-19 disease. Continuous education of personnel engaged in departments where COVID-19 patients are treated is very important in order to maintain awareness of standard operating procedures for infection control and implementation of preventive measures to prevent hospital infections. In the UKC RS, since the beginning of the epidemic, there has been continuous

education for all employees on the prevention of intrahospital infections, proper use of PPE, medical waste management and occupational health and safety.

Conclusion

There was no significant difference between SARS-CoV-2 positive and negative personnel, regarding the use and change of PPE, hand hygiene and surface decontamination.

Assessment of the occupational risk of exposure to SARS-CoV-2 can be determined based on the probability of coming into direct, indirect or close contact with infected persons, which implies direct physical contact or care, contact with contaminated surfaces or objects, contact due to medical procedures/procedures that generate aerosols on patients infected with COVID-19 without adequate protection, or working with the infected in closed, overcrowded rooms without adequate ventilation.

Proper use of PPE significantly contributes to the prevention of the emergence and spread of SARS-CoV-2. Assessment of the risk of exposure to SARS-CoV-2 at work takes into account the local epidemiological situation, specific characteristics of the work environment and tasks, the hierarchy of control measures and the level of adherence to infection prevention and control measures.

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Upotreba lične zaštitne opreme zaposlenih u COVID-19 odjeljenjima UKC Republike Srpske i procjena rizika od novog korona virusa

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Uvod. Procjena rizika izloženosti novom korona virusu radnika angažovanih u COVID-19 odjeljenjima Univerzitetskog kliničkog centra Republike Srpske i korišćenje lične zaštitne opreme su bili ciljevi ovog istraživanja.

Metod. U COVID-19 odjeljenjima Univerzitetskog kliničkog centra Republike Srspke (UKC RS), sprovedena je KAP studija (Knowledge attitudes Practice Study) kod 102 ispitanika svih obrazovnih profila upitnikom Svjetske zdravstvene organizacije (SZO), prilagođenim za ovo istraživanje, sa ciljem procjene rizika i postupanja u slučaju izloženosti radnika SARS-CoV-2 virusu. Anketiranje je bilo dobrovoljno i anonimno uz informisani pristanak ispitanika.

Rezultati. Od 102 anketirana ispitanika, njih 13 je bilo pozitivno na SARS-CoV-2 virus. Korišćenje kompletne LZO uvijek, kako je preporučeno, nosi 95,0% ispitanika. Način mijenjanja/uklanjanja LZO i dekontaminaciju kontaktnih površina uvijek provodi 88,2% ispitanika. Od 64 ispitanika, koji su koristili LZO u procedurama u kojima se generiše aerosol, njih 10 (15,6%) bilo je pozitivno na SARS-CoV-2, dok je njih 3 (7,9%), koji nisu učestvovali u procedurama u kojima se generiše aerosol, bilo pozitivno na SARS-CoV-2. Statistička obrada podataka rađena je u SPSS programskom paketu, verzija 20.0, uz nivo značajnosti razlike od 5% (p = 0,412).

Zaključak. Nije bilo statistički značajne razlike između SARS-CoV-2 pozitivnog i negativnog osoblja u odnosu na korišćenje i mijenjanje LZO, higijene ruku i dekontaminacije površina. Procjena rizika od izloženosti SARS-CoV-2 uzima u obzir nivo pridržavanja mjera prevencije i kontrole zaraze, specifične karakteristike radnog okruženja i zadataka, hijerarhiju kontrolnih mjera i lokalnu epidemiološku situaciju.

Ključne riječi: pandemija, novi korona virus, lična zaštitna oprema



Original article

Health care of COVID-19 positive pregnant women at the Clinic for Gynecology and Obstetrics of the University Clinical Center of Republic of Srpska

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Summary

Introduction. Corona-virus disease 2019 (COVID-19) is caused by heavy acute respiratory syndrome coronavirus 2 (SARS-CoV2) and represents the example of fast spreading disease. There has been a rapid increase of new and fatal cases since the virus was discovered in Wuhan, China, at the beginning of December 2019. Pregnant women are at a higher risk for the infection SARS-CoV2 and are prone to developing more severe clinical picture. Pregnant women with COVID-19 pneumonia mostly show different clinical pictures in comparison to the rest of the population.

Methods. There have been observed 184 COVID-19 positive pregnant women which were hospitalized in the period since the pandemic begun in Republic of Srpska. Included patients were treated at the University Clinical Center of Republic of Srpska and referred to this center from different parts of Republic of Srpska. The study was conducted from March 5th 2020 to March 15th 2022. Eight outcome parameters were observed in this study.

Results. During the observation period a total of 184 COVID-19 positive pregnant women were included in the study. An average age of patients was 30,63 years. An average duration of hospital stay was 8,90 days. A median of a gestation week of pregnant women was 37,5 weeks. The total number of patients in need of an oxygen support until a delivery was 18. All 18 pregnant women who were on an oxygen support delivered over a cesarean section.

Conclusion. COVID-19 brought a multitude of changes in clinical practice. However, COVID-19 is not an indication for a delivery change, as there are no evidences for favorization of one method of a delivery to the other one. A transmission of the infection from a mother to a child is possible but the cases of transplacental transmission remain scarce.

Key words: SARS-CoV2, COVID-19, pregnancy, pneumonia, newborns

Introduction

COVID-19 (Coronavirus Disease 2019) is a disease caused by a new coronavirus SARS-CoV2. Its rapid spread across the world became a huge challenge to health systems. The World Health Organization (WHO) proclaimed an urgent international situation on January 30th, 2020, and a global pandemics was announced on March 11th, 2020. The first case in Republic of Srpska was diagnosed on March 5th, 2020. Enormous efforts were invested into understanding of a virus and a disease in order to find efficient prevention methods, treatment strategy and finally developing a vaccine [1].

A virus transmission is dependent on close contact with an infected person or over the contaminated surfaces. The transmission by both droplets (aerosol) and feco-oral route are important. There has been alertness about the impact of COVID-19 on pregnant women and newborns. At the moment it is not elucidated if the virus spreads through ejaculate or vaginal discharge [2].

According to recent researches, a prognosis of the vast majority of pregnant women and newborns affected by COVID-19 is good. Many evidences show that pregnancy does not increase a risk for contracting SARS-CoV2, but clinical disease could take more severe course in comparison to non-pregnant women of the same age [3].

Complications of COVID-19 can lead to delivery complications. Risk factors in severe manifestations of COVID-19 infection in pregnant patients are pulmonary comorbidities, hypertension and diabetes mellitus. Pregnant women with severe COVID-19 have a higher incidence of cesarean section, premature delivery and their newborns are more often hospitalized in neonatal intensive care units [4].

After the COVID-19 infection is confirmed during pregnancy, a delivery is observed as potentially complicated. A choice of method of delivery should be individually adjusted. Generally, the recommendations for the delivery have not been subjected to change for women with confirmed infection [5].

It is advisable to test both symptomatic and asymptomatic pregnant women at admission due to high percentage of mild or difficult-to-detect cases. It is necessary to set special rooms or sections for pregnant women with a suspicion and/or confirmed infection of COVID-19, as well as decreasing the rotations of involved health staff. It is obligatory to wear adequate protective equipment [6].

All the world leading gynecologist associations recommend a vaccination against COVID-19 in a pregnancy. Immunization during a pregnancy protects a mother and a fetus from complications of a certain infection, also offers a passive protection to a newborn after a delivery. IgG antibodies peak four weeks after the immunization, while gestational age represents an important factor in regard to possibility of passive immunization which is beneficiary for fetus [7, 8].

The aim of this work was to examine the spectrum and effects of COVID-19 infection to a pregnancy outcome, both for a mother and her newborn.

Methods

This was a retrospective study conducted in the Clinic of Gynecology and Obstetrics of the University Clinical Centre of Republic of Srpska. A total of 184 COVID-19 positive pregnant women were observed since the beginning of pandemics in March 2020. The patients were admitted from different parts of Republic of Srpska to our tertiary care center. The study period ranged from March 5th, 2020 to March 15, 2022.

Our results included epidemiologic data on number of examined pregnant women with confirmed or suspected COVID-19, number of hospitalized patients due to this indication, a number of isolated patients and
prevalence of oxygen supplementation use in studied population. Following parameters and outcomes were observed during the study period: age of patients, a duration of hospital stay, choice of delivery method, presence of comorbidities.

Quantitative data are presented as absolute and relative frequencies. Quantitative data are further processed by a descriptive statistics. Pearson χ^2 test was used in assessment of frequency differences. Median values of multiple groups were compared by the use of Kruskal-Wallis test. For a comparison of median values for two independent samples (groups), a Mann-Whitney was used.

Statistical significance was set at p < 0.05.

For statistical analysis and data presentation IBM SPSS Statistics 23.0; MS Office Word 2016 and MS Office Excel 2016 were used.

Results

During the study period, a total of 184 COVID-19 positive patients (pregnant women) were admitted to the Clinic for gynecology and obstetrics of the University Clinical Center of Republic of Srpska. The average age of the patients was 30.6 years.

In the observed period four patients died with an average duration of hospital stay of 17 days (range 1-32 days) as presented in table 1.

An average period of hospital duration for all patients was 8.90 days, while median was 7 days. Patients discharged before delivery had significantly shorter hospital stay (median 5.5 days) when compared to patients who had deliveries before discharge (median 8 days) (Mann-Whitney's test z = -3.898, p = .000) (Table 2).

Table 1. Duration of hospital stay (days) for the COVID-19 patients at the Clinic for gynecolog	gy and
obstetrics of the University Clinical Center of Republic of Srpska	

Died	Ν	Minimum	Maximum	Median	Mean	Std. Deviation
Lethal outcome	4	1	32	17.50	17.00	12.987
Survived	180	1	48	6.50	8.72	7.330
Total	184	1	48	7.00	8.90	7.536

Table 2. Hospit	al discharge of	patients and ho	ospital duration (days)
	()			

Discharge before a delivery	Ν	Minimum	Maximum	Median	Mean	Std. Deviation
yes	98	1	27	5.50	6.81	4.843
no	86	1	48	8.00	11.28	9.204
Total	184	1	48	7.00	8.90	7.536

The graphic 1 shows a difference in duration of hospital stay (in days) for patients in regard to delivery.



Graphic 1. Hospital duration (days) of patients in a relation to the timing of discharge (prior or after the delivery)

In a group of 98 (53.3%) patients discharged before delivery oxygen support was applied in 19 (19.4%) cases. For 86 patients (46.7%) who had deliveries, supplementary oxygen was used in 18 (20.1%) (Table 3).

Table 3. Oxygen use in patients in regard to the timing of discharge (prior or after the delivery)

Discharge	Oxyger	Total	
Discharge	yes	no	Total
prior to delivery	19	79	98
after delivery	18	68	86
Total	37	147	184

Applying a χ 2test, with a correction according to Yates, showed that statistical significance difference was not achieved (χ 2 = .006, p = .939) when comparing these two groups of patients.

In all 18 COVID-19 patients treated at the Clinic until a delivery and receiving an oxygen

support, a cesarean section (CS) was applied – table 4.

Table 4. Delivery methods of COVID-19 patients

requiring overgon support

Delivery	Oxygen	Total			
Denvery	yes	no	TOtal		
Vaginal delivery	0	26	26		
Cesarean section	18	42	60		
Total	18	68	86		

Applying Fisher's Exact test, a high statistical significance of difference was achieved (p = .000), demonstrating that the COVID-19 patients requiring an oxygen support have significantly higher prevalence of cesarean section when compared to milder COVID-19 cases among pregnant women

At the time of cesarean section patients were in 35.7 weeks of gestation at an average. Patients requiring oxygen support were at an average in 33.06 gestational weeks, while patients without need of oxygen support were at average in 39.93 gestational weeks (Table 5). A gestation week median at the hospital admission for all the patients was 37.5.

Applying Mann-Whitney's test showed a high statistically significant difference (z = -3.533, p = .000) when comparing gestational week of patients undergoing cesarean section in relation to the need of an oxygen support: significantly earlier deliveries were performed in more severe, oxygen requiring cases of COVID-19.

Trombophilia as the isolated comorbidity was registered in 17 patients, and in association with hypertension in four patients and with diabetes in another four cases. Trombophilia was associated with other comorbidities in 11 patients. Other comorbidities were registered as isolated in 26 patients (15 patients with hypothyroidism was registered).

A presence of comorbidities was registered in a total of 68 (36.96%) patients; 16

Oxygen support	Ν	Minimum	Maximum	Median	Mean	Std. Dev.
Yes	18	26	39	34.00	33.06	4.193
No	42	27	41	39.00	39.93	3.809
Total	60	26	41	37.50	35.77	4.284

Table 5. Gestational week at the time of a cesarean section

(23.53%) out of this number required an oxygen support. A total of 37 patients had oxygen support with 16 (43.24%) of these having at least one comorbidity. Two out of three patients (63.04%) did not have any comorbidity, but 21 (18.1%) of patients received an oxygen support (Table 6).

Table 6. A presence of comorbidity in COVID-19 pregnant patients and the requirement of oxygen support

Comorbidity	Oxygen	Total	
presence	yes	no	TOtal
yes	16	52	68
no	21	95	116
Total	37	147	184

Applying χ 2test, with a correction according to Yates, statistical significance was not achieved (χ 2 = .484, p = .487) indicating that the presence of comorbidities did not affect the need for oxygen support in the studied COVID-19 pregnant patients.

Discussion

In our work, we analyzed data from the Clinic of Gynecology and Obstetrics of the University Clinical Centre of Republic of Srpska. A total number of admitted patients during the observation period was 184 COVID-19 positive pregnant women which an average age of 30,63, and an average hospital stay of 8,90 days. A median of a gestation week of all pregnant women in our work was 37,5 weeks. The total number of our patients in need of an ox-

ygen support until delivery was 18, and all of these where delivered by the cesarean section. During the 2020-2022 period, the COVID-19 pandemic dominated the obstetric health care. Unlike routine medical procedures, prenatal examinations and deliveries could not be postponed. At least 100 million babies were born during the pandemic, meaning that millions of women needed care during pregnancy, labor, and delivery, while performing antiepidemic measures [9]. Therefore, healthcare workers have made major adjustments to the healthcare delivery system to prevent COVID-19 infection. Along with basic hygiene measures such as disinfection and wearing protective clothing, more drastic measures, designed to prevent or slow contamination, included isolating patients with COVID-19, monitoring and contacting those infected or exposed, and enforcing social distancing [9].

Some studies show that pregnant women with COVID-19 showed to higher risk of severely symptomatic COVID-19 when compared to the non-pregnant women [10]. Additionally, women at late pregnancy have an increased risk of serious forms of COVID-19, which implies hospitalization, and even placement in an intensive care unit. The risk factors for a serious form of COVID-19 infection include being overweight, age over 35 years, and the existence of comorbidities [9].

Maternity staff is usually in close physical contact with pregnant and laboring women and are therefore, at high risk of infection, especially as infected pregnant women are often asymptomatic or have mild, difficult-to-detect Covid-19 infections [9]. Pregnant women should be regularly advised to stay at home minimally for two weeks before the predicted delivery term. For most of the women this period should start at 27th week of pregnancy. For women with suspicion or confirmation COVID-19 infection in an early pregnancy with complete recovery, a change of delivery term is not necessary. On the other hand for women with suspicion or confirmed COVID-19 infection in the third trimester who has not been recovered yet, it is reasonable to postpone a delivery (if other medical conditions allow this) until negative results of RT-PCR come back in order to prevent a virus transmission onto a newborn [11].

If there is no improvement of a clinical status, the early delivery should be planned. In a case of worsening of pregnant woman respiratory status or overall condition, further responsibility should be taken by the multidisciplinary team consisting of a gynecologist, anesthesiologist, intensivist and a neonatologist. All the decisions should include the consent of pregnant woman and her family [11]. For women with COVID-19 and pneumonia, who are not intubated, a delivery is considered at 32-34th gestational week [12].

For pregnant women with good clinical status and mild symptoms of COVID-19, a

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Ethical approval. The Ethics Committee of the University Clinical Center of Republic of Srpska approved the study and informed consent was obtained from all in-

vaginal delivery is safe and recommended while a cesarean cut is performed for standard medical indications. A newborn with COVID-19 is usually mildly affected, by requires a close monitoring in hospital setting [13]. A relatively small number of pregnant women were vaccinated against COVID-10, although there are evidence that a vaccine is safe both in regard to pregnancy and breastfeeding [14]. A great role during a delivery belongs to midwives, and their job grows more demanding during the pandemic era.

Conclusion

Pregnant women represent a vulnerable group during epidemics of infectious diseases due to specific physiology of pregnancy, sensitivity to infections. Maternal and fetal health must be additionally prioritized in these challenging circumstances. COVID-19 severely impacted health systems, affecting obstetric practices as well. As our data showed, severe COVID-19 in pregnancy, especially in patients requiring oxygen support, affects the timing of delivery and increases the probability of cesarean section.

dividual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Zdravstvena njega COVID-19 pozitivnih trudnica u Klinici za ginekologiju i akušerstvo Univerzitetskog kliničkog centra Republike Srpske

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Uvod. Bolest korona virus (COVID-19) uzrokuje teški akutni respiratnorni sindrom koronavirus 2 (SARS-CoV2) i predstavlja primjer brzo šireće bolesti. Došlo je do brzog porasta novootkrivenih i smrtnih slučajeva otkako je otkriven virus u Wuhanu, Kina, početkom decembra 2019. Trudnice mogu biti u većem riziku za infekciju sa SARS-CoV2 i mogu da razviju težu kliničku sliku. Trudnice sa upalom pluća COVID-19 pokazuju različite kliničke slike u poređenju sa ostalom populacijom.

Metode. Praćeno je 184 COVID-19 pozitivnih trudnica koje su hospitalizovane u periodu od početka pandemije u Republici Srpskoj. Uključene pacijentkinje koje su liječene u Univerzitetskom kliničkom centru Republike Srpske upućene su iz različitih dijelova Republike Srpske. Studija je provedena od 05. marta 2020. do 15. marta 2022. U istraživanju je praćeno 8 parametara.

Rezultati. Tokom posmatranog perioda, ukupno 184 COVID-19 pozitivne trudnice bile su uključene u istraživanje. Prosječna starost pacijentkinja bila je 30,63 godine. Prosječno trajanje hospitalizacije bilo je 8,90 dana. Medijana gestacijske nedjelje trudnica bila je 37,5 nedjelja. Ukupan broj pacijentkinja koje su zahtijevale kiseoničku podršku do porođaja bio je 18. Svih 18 trudnica koje su bile na kiseoničkoj podršci su porođene putem carskog reza.

Zaključak. COVID-19 donio je mnoge promjene u kliničkoj praksi. Međutim, COVID-19 nije indikacija za promjenu načina porođaja, jer ne postoje dokazi koji favorizuju jednu metodu porođaja u odnosu na drugu. Prenos infekcije sa majke na dijete je moguć, ali su slučajevi transplancentarnog prenosa vrlo rijetki.

Ključne riječi: SARS-CoV2, COVID-19, trudnoća, upala pluća, novorođenčad



Original article

Burnout syndrome and the quality of life of patients with diabetes mellitus and hypertension

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Summary

Introduction. The World Health Organization (WHO) defines burnout syndrome as a condition caused by chronic stress at work, which may be associated with the onset and worsening of psychosomatic illnesses and the quality of life of sufferers. The aim of the work was to determine the prevalence of burnout syndrome in the population of people with leading, chronic, massive, non-communicable diseases, type 2 diabetes and arterial hypertension, while assessing the impact of this syndrome on the quality of life of the subjects.

Methods. The research was conducted as a cross-sectional study from March 2019 until October 2019 on a randomized sample of 92 patients with type 2 diabetes and 99 patients with hypertension from two Health Centres in East Sarajevo. A special criterion for inclusion in the research was that the respondents were employed and that their age did not exceed 65 years. The research instrument was a general questionnaire, the WHO questionnaire on burnout syndrome, as well as the WHO SF-36 questionnaire on the quality of life, and statistical data processing was done in the SPSS program version 19.0. The significance of the difference was tested by the χ^2 test, and the existence of burnout syndrome was defined according to the WHO questionnaire.

Results. In subjects with diabetes, burnout syndrome was present in 52.8% (mildly expressed in 15.2% of the subjects, candidate for burnout syndrome in 19.6% of the subjects, burnout syndrome was present in 17.4%, while in one subject burnout syndrome that endangers health was found) and in subjects with hypertension, burnout syndrome was found in 32% of the subjects. Burnout syndrome was more present in subjects with diabetes than in subjects with hypertension. The difference was statistically significant ($\chi 2$ = 8.42; p = 0.003). Subjects with diabetes were significantly more depressed and discouraged than subjects in the group with hypertension ($\chi 2$ = 16.14; p < 0.01). The subjects with diabetes had significantly more difficulty in performing their job than those with hypertension during the past four weeks ($\chi 2$ = 13.098; p = 0.011).

Conclusion. There is a significant frequency of burnout syndrome in patients with diabetes, but also in patients with hypertension. The existence of cause-and-effect relationships significantly affects the quality of life of patients and their ability to work.

Key words: burnout syndrome, diabetes, hypertension, quality of life

Introduction

The World Health Organization (WHO) describes burnout syndrome "as a condition caused by chronic stress at work. Burnout syndrome is a prolonged response to chronic emotional and interpersonal stressors at work, and it is defined by the following dimensions: emotional exhaustion, cynicism (negative, dehumanized and insensitive attitudes towards people who are service recipients), depersonalization, lack of work involvement, low level of personal achievement and labour inefficiency" [1].

Burnout syndrome is a multidimensional chronic condition related to professional work that has consequences on the health and work ability of the sufferers. Many studies have investigated the possible connection between chronic stress at work and diabetes, as well as the quality of life of people with diabetes. Chronic stressors at work in people with diabetes are work overload, a sense of inequality and injustice manifested by the management of the company they work in, the possibility of job loss, conflicts at work and other work-related factors [2, 3].

Burnout syndrome, on the other hand, is associated with a disorder of the atherogenic lipid status in patients with diabetes, but it is also marked as a "trigger" for the onset of the disease. Several studies have found that duration of diabetes is associated with reduced quality of life in both types of diabetes, and most studies report that quality of life is worse in people with diabetes than in the general population, particularly in terms of physical functioning as opposed to social or mental aspects of quality of life. Studies examining more closely the specific domains of quality of life in people with both types of diabetes suggest that type 1 diabetes may be associated with limitations in physical health and current health perception, while in people with type 2 diabetes there may be reduced domains of physical functioning and limitations due to emotional problems and energy levels [4, 5, 6, 7].

The most common symptoms of burnout syndrome are: lack of energy, exhaustion, reduced work capacity, forced thoughts about work, deconcentration, reduced need for social contacts, emotional instability, muscle pain, dizziness [8].

Although burnout syndrome was originally associated with the profession of managers, and was often described as a "managerial disease", during many years of research it was found that the most common victims of burnout syndrome are employees in the health sector, but also those who work in direct contact with people or have direct responsibility for employees [9, 10].

Burnout syndrome has been the subject of many scientific researches since the 70s of the last century, so various measurement instruments have already been designed, such as several questionnaires used for that purpose [11]. The leading, mass, non-communicable diseases of today's civilization are diabetes and hypertension, which represent a huge health problem, both for the sufferers and for society as a whole [12].

Methods

The research was conducted as a cross-sectional study from March 2019 until October 2019 on a randomized sample of 92 patients with type 2 diabetes and 99 patients with hypertension from two Health Centres in East Sarajevo. A special criterion for inclusion in the research was that the respondents were employed and that their age did not exceed 65 years.

The research instrument was a general questionnaire, the WHO questionnaire on burnout syndrome, as well as the WHO SF-36 questionnaire on the quality of life, and statistical data processing was done in the SPSS program version 19.0.

The questionnaire on the quality of life SF-36v2 (Short form SF-36 ver 2) is used to measure the general quality of life. This questionnaire has 36 questions grouped into eight aspects (domains) of the quality of life. By further grouping the domains, two summary scores (physical and mental) are obtained. Coding of responses and calculation of domain values and summary scores is performed according to the SF-36 version 2.0 method in relation to the average population. The quality of life questionnaire includes eight domains of health: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health [13, 14, 15]. For the group of patients with diabetes, the summary scores were calculated: physical (PCS) and mental (MCS), and the average values of the summary scores were calculated. For the group of respondents with hypertension, the quality of life was not calculated according to the SF-36 questionnaire, so we compared the question about the quality of life that was asked for both groups of respondents according to the subjective assessment of the respondents and categorized them into three categories as: good, satisfactory and bad, whereby we used the $\chi 2$ test to test the difference. The significance of the difference for the occurrence of burnout syndrome between subjects with diabetes and subjects with hypertension was tested with the χ^2 test, and the

Table 2. Distribution of the subjects by gender

existence of burnout syndrome was defined according to the WHO questionnaire from 1997, which was designed for research on burnout syndrome.

The research was conducted in accordance with the ethical principles based on the Declaration of Helsinki and the relevant ethical committees approved the study, and all respondents gave their consent to be included in the study.

Results

The average age of the subjects of both groups is similar and not statistically significant (p > 0.05), so the groups are comparable in terms of age (Table 1).

Table 1. The average age of the subjects by groups

Group of subjects	Mean value	SD	Significance (p)		
Subjects with diabetes	55.08	8.281	NG		
Subjects of the control group	54.90	6.91	IN.5		
SD - standard deviation					

NS: not significant

NS. not significant

In the group with diabetes, there were 53.26% of male subjects and 46.74% of female subjects, and in the group with hypertension, 52.53% of male subjects and 47.47% of female subjects (Table 2).

Gender —	Subjects v	with diabetes	Subjects with hypertension		
	Number	Percentage (%)	Number	Percentage (%)	
Male	49	53.26	52	52.53	
Female	43	46.74	47	47.47	
Total	92	100.0	99	100.0	

The majority of respondents in both groups were in the occupational group from SE (secondary education) and HE (higher education) categories (Table 3).

In subjects with diabetes, burning syndrome is present in 52.8%, and in subjects with hypertension in 32% of subjects. The difference is statistically significant (χ 2 = 8.42; p = 0.003), relative risk (RR = 1.53, Confidence interval = 1.12–2.08) (Table 4).

For the group of patients with diabetes, the summary scores were calculated: physical (PCS) and mental (MCS), and the average values of the summary scores were calculated, which were: for PCS 42.6±9.8 and MCS 37.5±13.5. The obtained values indicate that the

quality of life (QOL) of subjects suffering from diabetes is significantly reduced compared to the QOL of the average population (50.0). The mental component summary (MCS) score is 1.25 SD lower than the population average, and the physical component summary (PCS) score is 0.74 SD lower than the population average. The minimum MCS value is 7.0, the maximum 65.0 producing a relatively large SD of 13.5, while the PCS values range from 20.4 to 62.6 with an SD of 9.8. According to the subjective assessment of their own quality of life, respondents suffering from diabetes do not differ from respondents with hypertension. The difference is not statistically significant $(\chi 2 = 3.472; p = 0.176)$ (Table 5).

Table 3. Distribution of the subjects by the type of occupation

Anorycon	Subjects	with diabetes	Subjects with hypertension	
Aliswer	Number	Percentage (%)	Number	Percentage (%)
Unqualified workers	11	11.9%	8	8.0%
SE - artisans and manual workers, drivers	14	15.2%	20	20.2%
SE - clerks	39	42.3%	49	49.4
HE - clerks	25	27.1%	21	21.2%
MA and PhD (officials and university teachers)	3	3.2%	1	1.0%
Total	92	100.0	99	100.0

Table 4. Distribution of the subjects according to the presence of burnout syndrome

FORM OF THE PRESENCE OF THE SYNDROME	Diab	etes	Hypertension	
TORM OF THE TRESERVE OF THE STROKOWE	Number	%	Number	%
Not present	43	46.7	68	68.7
Mildly expressed	14	15.2	9	9.1
A candidate for burnout syndrome	18	19.6	17	17.2
Burnout	16	17.4	4	4.0
Endangers health	1	1.1	1	1.0
Total	92	100.0	99	100.0

Quality of life —	Subjects with diabetes		Subjects with hypertension		
	Number	Percentage (%)	Number	Percentage (%)	
Good	8	8.7%	17	17.2%	
Satisfactory	50	54.3%	53	53.5%	
Bad	34	37.0%	29	29.3%	
Total	92	100.0	99	100.0	

Table 5. The subjects according to subjective assessment of the quality of	of life
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Table 6. The subjects who were discouraged and depressed within the past 4 weeks

Answer	Subjects v	with diabetes	Subjects with hypertension	
74150001	Number	Percentage (%)	Number	Percentage (%)
All the time	11	12.0%	3	3.0%
Most of the time	23	25.0%	21	21.2%
Half the time	15	16.3%	18	18.2%
A small part of the time	32	34.8%	26	26.3%
Not at all	11	12.0%	31	31.3%
Total	92	100	99	100

Table 7. The subjects who had difficulty performing work or other activities

Anguan	Subjects with diabetes		Subjects with hypertension	
Answer	Number	Percentage (%)	Number	Percentage (%)
All the time	20	21.7%	7	7.1%
Most of the time	24	26.1%	20	26.1%
Half the time	12	13.0%	24	24.2%
A small part of the time	19	20.7%	20	20.2%
Not at all	17	18.5%	28	28.3%
Total	92	100.0	99	100.0

Subjects with diabetes were significantly more depressed and discouraged in the past four weeks than subjects in the control group with hypertension. The difference is statistically highly significant ($\chi 2 = 16.14$; p < 0.01) (Table 6).

The difference between subjects suffering from diabetes and subjects suffering from

hypertension is statistically significant. The subjects with diabetes had significantly more difficulty performing work during the past four weeks than the subjects with hypertension ($\chi 2 = 13.098$; p = 0.011) (Table 7).

Discussion

This research examined the occurrence of burnout syndrome in a specific working population suffering from two massive, chronic, non-communicable diseases such as diabetes and hypertension. As it is well known that a huge number of the working population in the world suffers from these diseases. We tried to find a cause-and-effect relationship between the occurrence of these diseases and burnout syndrome at work as a special phenomenon described by the WHO as a condition caused by chronic stress at work. The question that arises during this research is whether these diseases are the cause of burnout syndrome or its consequence, given that it is known that both diseases have a psychosomatic basis that is characteristically associated with the existence of burnout syndrome [16].

Burnout syndrome is a multidimensional chronic condition that is related to professional work and has serious consequences on the health and work ability of the sufferers. Given that the examined group of the subjects had type 2 diabetes, the average age of the subjects was expected because the symptoms of this disease appear later in life [17]. The working ability of people suffering from diabetes is mainly reduced due to the underlying disease and its complications, so that the sufferers have reduced productivity at the workplace, increased work disability and increased absence from work, all of which affect the quality of life of the affected people, but at the same time lead to enormous costs for the health care system of the countries around the world [18, 19, 20].

Some of the basic symptoms that occur with burnout syndrome overlap with symptoms that occur as a result of diabetes. Thus, depression appears to be one of the main symptoms of burnout, but the connection between depression and diabetes has been proven in many studies. In our research, we found that respondents from the group with diabetes were significantly more depressed than the group with hypertension according to the SF-36 questionnaire on quality of life [21, 22].

The occurrence of burnout syndrome in the working population with diabetes is an additional burden factor on the already vulnerable category, both on their basic condition and on their ability to work. In several studies, the term burnout syndrome in diabetes is mentioned as a separate category that is not related to research of burnout syndrome in the general population, which is measured by a special questionnaire as an instrument highly specific for diabetes [23, 24]. In our research, among subjects with diabetes, the burning syndrome was present in 49 of them out of the total number of 92 subjects or 52.8%. From this percentage per category, we found a slightly pronounced burnout syndrome in 14 subjects with diabetes, or 15.2% of them. In the group that, according to the results of the questionnaire, is defined as a candidate for burnout syndrome, there are 18 subjects or 19.6% of them. Pronounced burnout syndrome was present in 16 respondents or 17.4% of them, while one respondent was diagnosed with a burnout syndrome endangering health.

In subjects with hypertension, the results were different than in the subjects with diabetes. Burnout syndrome was found in 31 subjects or 32% of them. Mildly expressed syndrome was found in 9 subjects or 9.1% of them. A candidate for burnout syndrome was found in 17.2% of the subjects. Pronounced burnout syndrome was present in 4.0% or 4 subjects, while one subject was diagnosed with a burnout syndrome endangering health. Although both diabetes and hypertension are chronic, massive, non-communicable diseases, in this study, subjects with diabetes had a much more pronounced burnout syndrome than subjects with hypertension.

In relation to occupation, in our research we found that 67 subjects with diabetes or 72.8% of them belonged to the category of white collar professions, which by nature of work were mostly sedentary occupations, while the remaining percentage of subjects with diabetes, 25 or 27% of them belonged to the category which, according to the valid research standards on burnout syndrome, was labelled as blue collar professions. Among subjects with hypertension, 71 subjects or 71% of them belong to the white collar profession category, while the remaining number of subjects are from the blue collar profession category. This data shows the undoubted connection of a sedentary lifestyle with the occurrence of chronic, massive diseases, such as diabetes and hypertension, and even burnout syndrome [25,5].

In a large number of studies, it has been confirmed that burnout syndrome can be a risk factor for the occurrence of type 2 diabetes, thus confirming the need to find effective primary interventions to reduce burnout syndrome before it becomes a chronic condition, thereby reducing the potential risk of damaging physical health [26, 27].

A study conducted in China on five thousand respondents showed that an increased degree of burnout syndrome was associated with chronic diseases such as diabetes, hypertension and coronary disease [29]. On the other hand, although the interrelationship of burnout syndrome with the occurrence of hypertension and coronary disease has been proven in several studies, there is a significant relation between burnout syndrome and other chronic diseases, primarily chronic lung diseases and skin diseases. All these studies show an undoubted relation between chronic diseases and stress, as well as stress at work, which the WHO characterizes as burnout syndrome [29, 30, 31].

The results of these studies comply with our research that there is a connection between the occurrence of burnout syndrome with diabetes and hypertension in affected persons and that this cause-and-effect relationship is an issue that arises as a significant problem of the working population due to the impact of this condition on the working ability of affected persons.

The relationship between work and health are interrelated categories, where work affects

health, but also health affects work. The effects can be immediate or delayed, where exposure to stress at work leads to later health problems. They can also be positive when the work directly or indirectly contributes to the health and well-being of the worker, or negative when the work leads to activity limitation, illness or even premature death of the employee. Individual work characteristics, but also their combined effect, can have a significant impact on the overall health status of each individual. All these effects can occur during an individual's working life or during retirement. The effects differ between individuals and depend on different individual and collective circumstances. According to data from the International Labour Organization (ILO), stress at work is the second most frequently reported work-related health problem in Europe. Exposure to a stressful, emotionally maladjusted and tiring work environment is associated with a higher frequency of fatigue and burnout at work, which on the other hand is associated with circumstances such as lifestyle, habits, ability to recover, access to healthcare services of employed persons. The International Labour Organization (ILO) pays a lot of attention to issues of health at work, and among other things, in recent years it has proposed specific programs and strategies to prevent the occurrence of stress in the workplace and to combat burnout syndrome as a phenomenon that directly affects the health of employees, their work ability and quality of life [32, 33, 34].

Conclusion

There is a significant frequency of the occurrence of burnout syndrome in patients with diabetes and hypertension. The existence of a cause-and-effect relationship between the occurrence of burnout syndrome and patients suffering from chronic, massive, non-communicable diseases significantly affects the quality of life of the patients and their ability to work. **Funding source.** The authors received no specific funding for this work.

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consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Sindrom profesionalnog sagorijevanja i kvalitet života oboljelih od dijabetes melitusa i hipertenzije

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Uvod. Svjetska zdravstvena organizacija (SZO) definiše burnout sindrom kao stanje prouzrokovano hroničnim stresom na poslu, što može biti povezano sa pojavom i pogoršanjem psihosomatskih oboljenja i kvalitetom života oboljelih. Cilj rada je bio da se utvrdi prevalencija burnout sindroma u populaciji osoba sa vodećim, hroničnim, masovnim, nezaraznim bolestima, dijabetesom tipa 2 i arterijskom hipertenzijom uz procjenu uticaja ovog sindroma na kvalitet života ispitanika.

Metode. Istraživanje je obavljeno po tipu studije presjeka od marta do oktobra 2019. godine na randomizovanom uzorku od 92 oboljelih od dijabetes melitusa tipa 2 i 99 ispitanika oboljelih od hipertenzije iz dva Doma zdravlja u Istočnom Sarajevu. Poseban kriterijum za uvrštavanje u istraživanje je bio da su ispitanici zaposleni i da nisu stariji od 65 godina. Instrument istraživanja je bio opšti upitnik, upitnik SZO o burnout sindromu, kao i upitnik SZO SF-36 o kvalitetu života, a statistička obrada podataka je rađena u programu SPSS v.19. Značajnost razlike je testirana <u>x</u>2 testom, a postojanje sindroma izgaranja je definisano prema upitniku SZO.

Rezultati. Kod ispitanika sa dijabetesom, burnout sindrom je prisutan kod čak 52,8% (blago izražen kod 15,2% ispitanika, kandidat za burnout sindrom kod 19,6% ispitanika, burnout sindrom prisutan kod 17,4%, dok je kod jednog ispitanika utvrđen burnout sindrom koji ugrožava zdravlje), a kod ispitanika sa hipertenzijom burnout sindrom je nađen u procentu od 32% ispitanika. Burnout sindrom je bio više prisutan kod ispitanika oboljelih od dijabetesa nego kod ispitanika sa hipertenzijom. Razlika je statistički značajna ($\chi 2 = 8,42$; p = 0,003). Ispitanici sa dijabetesom su bili značajno više depresivni i obeshrabreni od ispitanika kontrolne grupe sa hipertenzijom ($\chi 2 = 16,14$; p < 0,01). Ispitanici sa dijabetesom su značajno više od ispitanika sa hipertenzijom imali teškoća pri obavljanju posla tokom protekle 4 nedjelje ($\chi 2 = 13,098$; p = 0,011).

Zaključak. Postoji značajna učestalost pojave burnout sindroma kod oboljelih od dijabetesa, ali i hipertenzije. Postojanje uzročno-posljedične veze značajno utiče na kvalitet života oboljelih i njihovu radnu sposobnost.

Ključne riječi: burnout sindrom, dijabetes, hipertenzija, kvalitet života



Case report

Mild early course of osteogenesis imperfecta type XIV - a case report

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Summary

Introduction. Mutations in TMEM38B gene, which encodes the endoplasmatic reticulum membrane trimeric intracellular cation channel (TRIC) type B, cause osteogenesis imperfecta type XIV. So far there have been only four different pathogenic variants reported in TMEM38B. Clinical features of osteogenesis imperfecta type XIV described in scarce reports include osteopenia, femoral bowing, low trauma fractures, scoliosis, muscular hypotonia and cardiac pathology.

Case report. A 2-month-old male infant was referred to a clinical geneticist office due to bone deformities. The shortening of the limbs was observed during the prenatal ultrasound examination in seventh month of pregnancy. Prenatal cytogenetic analysis was performed from a fetal blood sample and showed normal findings. Neither fetal fractures were observed prenatally, nor any occurred during vaginal labor. During the first clinical exam by the clinical geneticist, discrete rhizomelia and bluish sclerae were observed. Due to the suspicion of skeletal dysplasia, indication for genetic analysis was established. Next generation sequencing panel for skeletal dysplasia showed homozygous deletion of exons 1 and 2 in the TMEM38B gene, confirming osteogenesis imperfecta type XIV. At the follow-up visit performed at 12 months of age, no fractures were reported. Several skeletal deformities were observable: discrete frontal bossing, rhizomelic upper extremities, slightly bowed thighs and shins. The infant achieved normal psychomotor development. A radiographic examination showed bowing of long bones of the lower extremities, without significant osteopenia.

Conclusion. Absence of early fractures is rare in osteogenesis imperfecta type XIV. Relatively mild clinical features of our patient therefore contribute to the understanding of the phenotype of osteogenesis imperfecta type XIV and its relation to the genotype.

Key words: skeletal dysplasia, TMEM38B gene, deletion

Introduction

Osteogenesis imperfecta represents a group of heritable disorders of connective tissue with an estimated prevalence of 1:10.000 to 1:20.000 live births [1]. Main clinical features of osteogenesis imperfecta include bone fragility, recurrent fractures, bone deformities, dentinogenesis imperfecta (DI) and growth deficiency [1]. Also, different extra-skeletal manifestations could be found in these patients, such as blue sclera, hearing loss, joint hypermobility and cardiovascular complications [2]. As of 2021, 20 types of osteogenesis imperfecta have been defined [3]. Types I-IV are autosomal dominant disorders caused by defects in the COL1A1 and COL1A2 genes that encode type I collagen and account for about 75-85% of cases [4, 5]. Rare forms of osteogenesis imperfecta (types V-XXI) are caused by mutations in genes associated with post-translational modification of type I collagen and are mostly inherited in autosomal recessive manner, with exceptions of type V (autosomal dominant) and type XIX (X-linked recessive) [5]. Mutations in TMEM38B gene, which encodes the endoplasmatic reticulum membrane trimeric intracellular cation channel (TRIC) type B, cause osteogenesis imperfecta type XIV [6]. TRIC-B channel is involved in the release of calcium ions from intracellular stores [7, 8]. So far there have been four different pathogenic variants reported in TMEM38B: a deletion in exon 4 found in Saudi Arabians and Israeli Bedouins [6, 9], a point mutations in exon 4 and intron 3 found in Chinese children [10], and a deletion of exons 1 to 2 found in an Albanian child [11]. Clinical features of osteogenesis imperfecta type XIV described in scarce reports include osteopenia, femoral bowing, low trauma fractures, scoliosis, muscular hypotonia and cardiac pathology [6, 9–12].

The aim of our report is to describe a patient with mild phenotype of extremely rare form of osteogenesis imperfecta,

Case report

A 2-month-old male infant was referred to a clinical geneticist office due to bone deformities. The shortening of the limbs was observed during the prenatal ultrasound examination in the seventh month of pregnancy. Prenatal cytogenetic analysis was performed from a fetal blood sample and showed normal finding. No fetal fractures were observed prenatally, nor any occurred during vaginal labor. Body weight at birth was 2800 g, body length was 48 cm, while Apgar score was 9/10. Hearing screening showed a normal finding.

During the first clinical exam by the clinical geneticist, discrete rhizomelia and bluish sclerae were observed. Due to the suspicion of skeletal dysplasia, indication for genetic analysis was established. Family history was negative for skeletal disorders (short stature, deformities or recurrent fractures). Consanguinity was negated by the parents, but could not be excluded due to same ethnic background in relatively small community.

Next generation sequencing panel for skeletal dysplasia was performed at CeGaT laboratory in Tubingen (Germany), and showed presence of homozygous deletion of exons 1 and 2 in the TMEM38B gene (NM_018112.3(T-MEM38B):c.454+279_543-5092delinsAATTA-AGGTATA). This finding confirmed the diagnosis of osteogenesis imperfecta type XIV.

At the follow-up visit performed at 12 months of age, no fractures were reported. Several skeletal deformities were observable: discrete frontal bossing, rhizomelic upper extremities, slightly bowed thighs and shins. The infant achieved normal psychomotor development. Findings in other organ systems were normal, apart from blue sclera.

A radiographic examination of the upper extremities, spine, pelvis and lower extremities was performed, which showed bowing of long bones of the legs (Figure 1). All bones were of preserved continuity, with no signs



Figure 1. X-ray findings in a male infant with osteogenesis imperfect atype XIV: A. bowed long bones of the legs, B. Femoral bowing without other significant skeletal abnormalities

of fresh or old fractures. Also, radiographs did not show significant demineralization of the skeleton.

Discussion

When compared to the only osteogenesis imperfecta type XIV patient previously reported with the same genotype (homozygous deletion of exons 1 and 2 in TMEM38B), our patient has a milder clinical picture [11]. Namely, a girl of Albanian origin reported by Rubinato et al. had seven fractures already at birth, while our patient did not have any conatal fractures. Also, they did not occur during first year of life. Additionally, our patient did not show significantly reduced bone mineralization. A mild conductive hearing loss that was observed in a previously reported patient with the same genotype was absent in our patient. Additionally, in this Albanian girl bone deformities were not recorded, while the infant boy we are reporting herein has bowed limbs. It is important to note that the girl was diagnosed at the age of 10, and that the examination was preceded by surgical interventions due to numerous fractures, as well as bisphosphonate therapy. Also, fetal ultrasound exam was missing in case described by Rubinato et al. Similarities between these two patients are the normal psychomotor development and absence of cardiac involvement. Both patients homozygous for deletions of exons 1 and 2 in TMEM38B are of Albanian ethnic background and come from rural communities with possible consanguinity. Differences in fracture incidence between patient reported by Rubinato et al. and our patient could be attributed to the influence of an unknown modifier gene. Data on labor circumstances for the patient from literature [11] are not available, and presence of several fractures could be caused by prolonged vaginal labor or abnormal birth presentation. In our patient no fractures were recorded at birth despite the vaginal labor.

Two patients carrying the aforementioned deletion in heterozygous state have been reported to have British-American and British-German heritage [12]. These patients also displayed normal motor and cognitive development.

Lack of cardiac involvement in patients homozygous for deletions of exons 1 and 2 in TMEM38B could be of importance since different cardiac abnormalities including congenital septal defects, tricuspid regurgitation, non-obstructive hypertrophic cardiomyopathy and early myocardial infarction have been described in more than a third of osteogenesis imperfecta type XIV patients reported by Webb et al. [12].

Blue sclerae are well known sign of inherited connective tissue disorders and one of the hallmarks of osteogenesis imperfecta. Blue sclera was noted at the first clinical geneticist examination of our patient at two months of age. However, this clinical sign is not universal in osteogenesis imperfecta type XIV since several authors report majority of their patients lacking the bluish sclera appearance (China, Israel). Furthermore, the patient with the same homozygous deletion of exons 1 and 2 did not show blue sclera [11]. This difference in comparison to the patient we report could be related to the age of first detailed evaluation.

Low trauma fractures during the first two years of age have been verified in more than 90% of the reported patients with osteogenesis imperfecta type XIV [6, 9–12]. Lack of fractures during infancy observed in our patient seems to be uncommon in this type of osteogenesis imperfecta. However, at least one reported patient homozygous for mutations in TMEM38B remained asymptomatic [12].

Prenatal ultrasound findings were the very first sign of osteogenesis imperfecta type XIV in our patient. Short and bowed extremities, decreased mineralization and prenatal fractures have been reported as the hallmarks of ultrasound exam in fetuses with early onset types of osteogenesis imperfecta [13, 14]. Therefore, such findings of fetal ultrasound screening should prompt genetic evaluation due to high risk of skeletal dysplasia.

Genetic tool employed postnatally in the diagnostics of our patient was the panel for osteogenesis imperfecta and related skeletal dysplasias with decreased bone density provided by CeGaT GmbH, Tübingen, Germany, that sequenced 30 genes of interest, with turnaround time of less than four weeks. A recent study showed whole exome sequencing established a genetic diagnosis in 15.4% of fetuses with skeletal dysplasia. The same study showed that diagnostic yield of prenatal WES was higher for skeletal dysplasia when compared to other indications. Other studies showed even greater benefit from whole exome sequencing employed both in prenatal and postnatal setting, especially if targeted gene panel for skeletal disorders was used [15].

Conclusion

Clinical and radiographic features of our patient contribute to the understanding of the phenotype of very rare type of osteogenesis imperfecta and its relation to the genotype. Early genetic diagnosis provides possibility to plan specific follow-up, treatment strategy and adequate genetic counseling. **Funding source.** The authors received no specific funding for this work.

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Conflicts of interest. The authors declare no conflict of interest.

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Blagi rani tok osteogenesis imperfecta tip XIV – prikaz slučaja

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Uvod. Mutacije gena TMEM38B koji kodira trimerički intraćelijski katjonski protein tip B (TRIC) endoplazmatskog retikuluma, uzrokuju autozomno recesivnu osteogenesis imperfecta tip XIV (osteogenesis imperfecta tip XIV). Do sada su opisane svega četiri patogene varijante u navedenom genu. Kliničke karakteristike u malobrojnim radovima o osteogenesis imperfecta tip XIV uključuju osteopeniju, zakrivljenost femura, patološke frakture, skoliozu, mišićnu hipotoniju i promene na srcu.

Prikaz slučaja. Dvomesečno muško odojče je upućeno na pregled kliničkog genetičara zbog deformiteta kostiju. Skraćenje ekstremiteta je bilo vidljivo prilikom prenatalnog ultrazvučnog pregleda u sedmom mesecu gestacije. Prenatalna citogenetička analiza je bila uredna. Nije bilo fetalnih fraktura, niti su se dogodile tokom porođaja. Pri prvom pregledu kliničkog genetičara registruju se diskretna rizomelija i plavičasta prebojenost beonjača. Zbog sumnje na koštanu displaziju sprovedena je genetička analiza panela gena sekvencioniranjem nove generacije i utvrđena je homozigotna delecija egzona 1 i 2 u TMEM38B genu, čime je postavljena dijagnoza osteogenesis imperfecta tip XIV. Na kontrolnom pregledu u uzrastu od 12 meseci, dobija se podatak da nije bilo fraktura. Uočavaju se diskretni koštani deformiteti: naglašeni frontalni tuberi, rizomelični gornji ekstremiteti i lako zakrivljene natkolenice i potkolenice. Dete ima uredan psihomotorni razvoj. Radiografski nalaz je pokazao zakrivljenost kostiju nogu bez značajne osteopenije.

Zaključak. Odsustvo patoloških preloma u ranom uzrastu se susreće kod većine pacijenata sa osteogenesis imperfecta tip XIV. Stoga, blaži klinički tok kod našeg pacijenta doprinosi boljem razumevanju fenotipa ove retke bolesti i njegovog odnosa prema genotipu.

Ključne reči: skeletna displazija, TMEM38B gen, delecija



Review

The influence of social isolation during the COVID-19 pandemic on speech and language development in preschool children

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Summary

Speech is a way of communication formed by rhythmic units of syllables, words and sentences, and as such is inherent in man, the only being whose organs and psyche are trained for this process. Delayed speech is defined as a phenomenon in which a child does not start speaking on time, or there are errors in the speech pattern that are not appropriate in relation to a given age. It is known that significant risk factors for the development of delayed speech in preschool children are physical, and most often social and emotional in nature. For the normal development of speech, it is necessary that the child is in a human environment, and therefore the circle of people with whom children come into contact should always be expanded.

The aim of this study is to review the existing literature on studies examining the impact of social isolation during the COVID-19 pandemic on preschool children, as well as the speech and language development in preschool children.

The recent pandemic of corona virus infection (COVID-19) has led to a state of emergency, quarantine, closure of public institutions, and preschools, kindergartens and schools in 172 countries. These epidemiological measures have led to social isolation and the need for children to learn from home, which has manifested itself in the emergence of difficulties in the development of speech and language. Research has shown that during the pandemic, children spent significantly more time watching television and computer screens than before pandemic, and less in play and physical activity.

Keywords: speech, speech development, social isolation, COVID-19 pandemic, preschool children

Introduction

Speech can be defined as normal fluency [1]. This fluency is understood as the ability to speak with normal continuity, degree, and effort. We communicate in order to satisfy our desires, reveal our feelings, share information and achieve a set goal [2]. Speech plays an important role in people's lives and due to the complex process and early development

of speech in children, awareness of parents, guardians and the environment on how to help children and encourage their speech development, as well as overall development, is also important. By talking to the child, parents build and supplement the child's knowledge. The conversation directs him/ her to independent thinking and reasoning [3]. In the preschool period, children should not only be taught how to speak, but also to communicate in a cultural way with adults and their peers, by learning to listen to the speech of the interlocutor [4]. Petz [5] states that speech includes all types of letters, all forms of mimic and gestural communication, as well as the use of various communication signals. Also, speech facilitates the psychological function of thinking, because words are symbols with a certain meaning, and in that way concrete and abstract concepts are created. Language disorders are defined [6] as all forms of disorders in speech and language functioning that, in any way, interfere with communication and have an impact on psychosocial development or are otherwise related to it. Known risk factors for the development of language disorders and speech retardation in preschool children are physical, and most often social-emotional factors [2]. Physical causes are usually disorders of the organs that enable speech (rabbit's lip, irregularly spaced teeth, cleft palate) [2]. The cause can also be a multilingual family environment, a family history of slow speech development, a low level of parental education and inadequate stimulation for speech development by parents or guardians [7]. In the literature [8], it is known that speech will not occur without the influence of the social environment. For the normal development of speech, it is necessary for the child to be in a human environment, and therefore the circle of persons with whom children come into contact should always be expanded. Such experiences encourage speech and communication skills in children. In addition to the

significant influence of the child's parents on speech development at the beginning of the preschool period, peers have the most significant influence on speech development in the second half of the preschool period [9, 10]. That is why this review work is planned so that we can see whether the pandemic of coronavirus infection (COVID-19), particularly isolation during the pandemic, had an effect on slow speech development in preschool children. Given that it has been shown that the COVID-19 epidemic is not only a health crisis, but also affects social and economic trends, thus causing numerous consequences for the lives of adults and children - the starting idea of this research is to examine these consequences. This research would have a significant, both scientific and social aspect. Although it is known from the literature that the causes of slow speech development can be physical, emotional, as well as social factors such as parental educational status, time spent with the child or excessive exposure of children to filming [7], so far relatively few research examined whether the social isolation caused by the COVID-19 pandemic could have an impact on the occurrence of slow speech development.

Speech development

It is important for every parent to know the stages and norms of speech and language development in order to be able to consciously monitor the child's progress, encourage him/ her to pronounce words correctly, and to be able to assess at any time whether speech develops properly and whether there are potential deviations in this area of development. The first vocalization that a child realizes is crying and this is the beginning of later speech. After that, the child gradually learns to use the speech of the people around him, ie. he/she tries to make the sound as similar as possible to the one he/she hears. In this way, the child learns by repetition, ie to pronounce certain words after another person [11]. Speech development in children is influenced by biological (organic), psychological and social factors [2]. The influence of the environment is very important, because without it, speech could not even develop. That is why it is important to raise awareness of the environment about the importance of its impact on the psycho-physical development of the child, as well as its positive effect and encouragement of speech in everyday situations [12]. The family, as the child's most natural environment, is the most important factor in speech development, as in other areas of development [10]. Starc et al. [13] state that the critical period in which children begin to speak is the period from 18 to 24 months after birth. Also, these authors state that sensitivity to speech development is associated with the development of the central nervous system, and especially with structural changes in the brain, ie. a sudden increase in brain mass, and the number of synapses between nerve cells between certain regions of the brain. It is very important that in this period of life the child has adequate social stimulation, because that is the only way to get to the use of innate possibilities and speech development. Also, in addition to this period when speech begins to develop, the preschool period of child development is very important, ie the period from 2 to 7 years of age, which is considered the most important period for speech development, because at that age the child absorbs every year more and more content from the environment and begins to learn and adopt the grammatical rules of the language, and increasingly shapes its linguistic level of speech expression [14, 15].

Although communication encompasses more aspects than language and speech, it is very important to distinguish these concepts. The psychological dictionary defines language [5] as a system of signs by which people communicate, and this system realizes the function of communication. Language significantly helps the psychological function of thought and registers personal experiences. Language also preserves memorized information and experiences, so in that way it enables the use of other people's eyes and ears so that one can learn not only from one's own, but also from other people's experiences [16]. Language consists of five aspects of communication: voices, meanings, forms and word order, as well as the social use of language [17].

Speech consists of two key components, sending and receiving messages, therefore, the speech organs include those that create speech, as well as those that receive information and enable understanding of speech [15]. We have divided the speech organs that create speech into movable and immovable. The moving organs important for voice formation are: larynx, vocal cords, palate, tongue, lower jaw, pharyngeal walls, and lips. The immobile organs important for the formation of the voice are: the hard palate, the upper jaw and the teeth. The voice is created by the sound current passing from the lungs through the trachea, then passing through the larynx with the vocal cords - this is where we get the shape of the voice. Once the voice reaches the throat over which the pharynx is located, the voice goes through the nasal and oral cavities. These cavities have the function of resonators, ie they help to amplify or reduce the voice. In these cavities, the air flow takes on its final shape [18-25].

Speech and language disorders

Speech disorder is a disorder in which the child, at the age when certain sounds need to be pronounced, cannot speak some sounds adequately and standardly for the native language due to various reasons, mixes or omits them, and does not pronounce syllables or whole words correctly, while his/her language and vocabulary are grammatically correct and meaningful [17]. We have divided all speech and language disorders into several categories, namely: slowed speech and language development, pronunciation disorders, dumbness and deafness, rhythm and tempo disorders, ie. speech fluencies (stuttering, bradylalia, battarismus), dyslalia, reading and writing disorders and voice disorders [12, 15, 26, 27]. Also, a special entity of speech disorders is a pronunciation disorder that can occur in three forms, such as the absence or realization of a voice that is not heard (omission): the child cannot pronounce a voice at all (eg. instead of book the pronunciation is "boo", instead of pronouncing pig pronounces "pi"), substitution of voices (substitution): the child replaces one voice or set of voices that he/she cannot pronounce with another voice (eg. instead of a rabbit, he/she pronounces "wabbit"), incorrect pronunciation of a voice or a set of voices (distortion): the child utters voices, but their sound realization deviates from the standard pronunciation ("thith" instead of this) [14]. The causes of slow speech development in children of the typical population are not fully known. However, several factors could play a significant role [28-30].

When we notice a delay in speech and language development in a child under the age of four, then we can talk about a slow development of speech and language. Slowed speech and language development can be observed in a child up to the age of four [15, 26]. However, if the difficulties continue after the fourth year of life, then we are talking about underdeveloped speech. Underdeveloped speech can be recorded if the child speaks less than his/her peers or speaks much later, uses a limited number of words, often uses a word order that is unusual, simpler and shorter sentences, or has difficulty understanding language or speech messages. A child who lags behind in speech and language development, in a large number of cases will lag behind in other segments such as motor skills, coordination of movements, graphomotor skills and insecurity in left-right relationships [26]. After the parent or the child's environment notices deviations in speech and language development, from the norms for a given calendar age, it is very important to contact on time professionals involved in the prevention, diagnosis and treatment of speech, voice, language disorders, and all other forms of communication, namely speech therapists. Speech therapists are the most competent in determining whether a child really has a problem with speech and language, and the examination of speech ability is conducted with the help of non-standardized and standardized tests. Research has shown that 5% to 10% of children have more serious speech difficulties that require professional help [17]. Therefore, it is not important to just assess what a particular child can do at a given moment, it is just as important to know what it can do in the future, how he/she will further develop his/her cognitive skills. From the perspective of socio-cultural theories as which is Vygotsky's theory in this sense, it is a significant concept of the zone of further development, that is, it is necessary to distinguish between what the child can do independently and what he/she can achieve with the help of a competent adult [30].

COVID-19 virus pandemic

In December 2019, a series of cases of viral pneumonia of unknown cause appeared in Wuhan, Hubei, China. The World Health Organization [31] was the first to report cases of pneumonia of unknown origin in the city of Wuhan, and the occurrence of the disease was associated with the use of products from the local market for the sale of animals and seafood. However, the infection soon spread and reached pandemic proportions, so that a pandemic was declared on March 11, 2020 [32].

Detailed sequential analysis from samples of the lower respiratory tract identified a new virus called SARS-CoV-2, which causes coronavirus infection (COVID-19). The clinical picture of COVID-19 infection ranges from asymptomatic or mild forms with respiratory symptoms: fever, cough, shortness of breath, difficulty breathing, loss of sense of taste and smell, to severe forms: :pneumonia, severe acute respiratory syndrome (Engl. Acute Respiratory Distress Syndrome -ARDS), multiorgan failure and even fatal outcome [33, 21, 34]. Risk factors for the development of severe forms of COVID-19 disease are older age, obesity, as well as previous chronic diseases and conditions [35, 34]. According to WHO data [23] until 06.03.2022. a total of 433 million people became ill, while 5.9 million people died from the effects of COVID-19 worldwide [23]. At a time when everyone is talking about the COVID-19 virus pandemic and its spread, it is expected that children partially know what is happening and that they feel scared, confused and anxious due to a sudden change in lifestyle [36]. By encouraging conversation with the child, parents get the opportunity to correct all the information that is not necessarily verified or true. A special problem in this situation is the fact that during the COVID-19 pandemic, parents must continue to go to work (health workers, workers in state institutions), so children stay with other family members who keep them at home [33, 35]. The proper treatment of children by their parents is to provide them with accurate information, but also to adapt it to the child's age, to limit children's exposure to information from the media and to try to create a fun, positive atmosphere at home. From the scientific point of view, it is interesting to show whether the literature data confirm that isolation during the COVID-19 pandemic led to slow speech development in preschool children, and from the social point of view to draw public attention to the possibility of applying certain measures if society finds itself in this situation again.

Aim and methodology

The aim of the study is to review the existing literature to present studies that examined the impact of social isolation during the COVID-19 pandemic on the development of speech and language of preschool children, with special emphasis on the nature and type of that impact.

The Google Scholar browser, SCIndex, the ProQuest browser and the service of the Consortium of the Library of Serbia for Unified Procurement (KOBSON) were used to search the existing literature. Studies in mother tongue and English were searched. The key words were speech, speech development, social isolation, the COVID-19 pandemic, and preschool children. The studies are further selected on the basis of key words in the title or abstract of the study. After reviewing the available literature, theoretical and review studies have been excluded, and studies which in their research studied the impact of the COVID-19 pandemic on preschool children and on their speech and language development have been presented.

The impact of the COVID-19 virus pandemic on preschool children

The COVID-19 pandemic has led to significant economic and social challenges in the world. National authorities around the world responded to the pandemic relatively quickly by introducing a state of emergency, quarantine, closure of public institutions, social distance, travel restrictions and increased control of work in the workplace. Preschools, kindergartens, schools and universities were closed in 172 countries, affecting 98.5% of the child population who had previously attended some of these institutions [37]. These conditions of extensive restriction in social relations in schools have led to the fact that children have spent a lot of time at home with their families. The United Nations Educational, Scientific and Cultural Organization has stated that one of the most significant risks that school closures due to a pandemic can cause is "interrupted learning" which affects children's mental and physical health and that this disruption is one of the most harmful consequences of a pandemic [38]. The COVID-19 pandemic and the social isolation caused by the pandemic significantly affect daily activities in all aspects of a child's life, and there is a particularly negative effect on children's growth and development [20, 39]. Although preschools and schools have resumed operations after the closure period, what has remained is the concern how the COVID-19 pandemic will affect the younger population. Research done during earlier epidemics and pandemics has shown that the negative effects of a pandemic on children's development will occur immediately and later, with a particularly high risk in early childhood, when brain architecture is still developing rapidly, it is not fully formed and it is very sensitive to difficulties from the environment. Previous data show that the pandemic has significantly affected children's learning capacities, physical and mental health, adaptive behavior, and productivity [40]. In education, generations of children have realized that their education has been abruptly interrupted. It is estimated that during the pandemic, classes were interrupted for 1.59 billion pupils and students - or 91% of pupils and students worldwide [41, 42]. The effect of closing kindergartens, preschools and schools on the level of children's education remains unknown, however, the consequences for younger children, on their growth and development are already beginning to appear. Interruption of formal education can cause a negative effect on a number of children of younger calendar age in the form of learning difficulties, especially in children who are at a disadvantage and do not have equal access to information [37].

Social isolation in the form of quarantine, social distancing and increased use of masks

are measures proposed by the World Health Organization [32] for children who are exposed to or infected with the corona virus in order to prevent its spread. Although these protective measures are necessary, they can have adverse effects on children's speech and language, as well as the development of communication skills during a critical period of growth and development. It was mentioned that social interaction is necessary for the development of speech and language, and epidemiological measures of distancing and prohibition of group gatherings have influenced preschool and school age children to be limited in interactions with peers [43].

In most countries, the alternative to formal education during the pandemic was to continue learning and monitoring classes with the help of electronic devices from home. However, most preschool children are not able to read independently, and reading aloud to children of this age significantly affects the formation of their speech and language [44]. In addition, the closure of educational institutions leads to social and emotional problems of children such as significantly fewer hours of sleep, poorer nutrition, more time spent on electronic devices, less physical activity, development of higher levels of stress, and all this can significantly contribute to physical and mental health of children [29]. These results are confirmed by data stating that the COVID-19 virus pandemic has put children at risk for the development of fear of illness, social isolation, prolonged confinement indoors and increased stress levels of parents or guardians of children [40]. This situation has a negative impact and can cause stress in children, which can result in poorer neurological development, negative effect on physical and mental individual and collective health, cognitive abilities, as well as work habits and abilities of future adults.

The COVID-19 pandemic is an unprecedented situation in which all systems of society are suddenly affected at the same time, and adapting to the new reality and habits is expected to be a difficult task, especially for younger children, especially if they already have developmental disabilities. The pandemic has led to changes in society, and in every household, which are difficult for children to understand. These changes in normal daily activities can lead to frustration and anxiety in children, especially if there is some form of developmental, speech, language, or communication disorder [45].

Research overview - the impact of the COVID-19 virus pandemic on speech development in preschool children

Kyle and co-workers [46] found back in 2013 that wearing protective masks significantly reduced the intensity of the speech signal, especially for high frequencies, and the level of attenuation ranged from 3 to 4 dB when it came to surgical masks, and about 12 dB for KH95 masks. This change in the intensity of the speech signal can affect speech comprehension in children who have speech disorders or some hearing disorder when compared to peers who do not have these problems. Harding et al. [47] state that the use of masks and protective equipment by parents and health care workers can have a negative impact on the mental development of children with whom they come into contact in health care institutions. These protective measures limit contact and reduce the possibility of connecting parents and infants, and can potentially negatively affect the establishment of breastfeeding and the physiological stability of infants. Wearing masks limits mother-child contact and prevents the child from watching and cooperating with the parent, which is part of every child's early learning and research. These limitations could delay the learning necessary for the timely development of communication. These authors state that it is important to regularly apply certain strategies of interaction between parents

and children in order to encourage the development of speech, language and communication. Some of the strategies proposed by Harding et al. [47] are to use voice and change in voice intonation in interaction with children, use gestures in interaction to encourage the development of gestural communication, and use masks with transparent or plastic slits so that the child can, when he/she wishes, see the expression on the parents' faces and the movements of the parents' speech organs during speech. Reading books aloud to preschool children by parents is recommended as one of the best alternatives for the period during the social isolation caused by the pandemic, given that children of younger calendar age have limited ability to read independently. In addition, the vocabulary from books, which children listen to when parents read, is composed of more complex sentences in relation to telling stories to children or in relation to everyday conversation. Also, one of the advantages of reading to children is that it can help them practice reading words with their parents and interact with the text from the book, asking parents questions about what they do not understand, which significantly contributes to better speech and language development.

A study by Darmiyanti et al. [48] conducted in Indonesia examined the impression of 400 parents and teachers on the impact of the COVID-19 pandemic on the language and speech development of children aged 4 to 6 whose formal education was interrupted for 8 months. The authors examined receptive skills (listening and reading) and productive language skills (speaking and writing), with special reference to listening and speaking. The results of the study showed that only 165 respondents (41%) could achieve the goal of curriculum in mastering language skills prescribed by the Ministry of Education and Culture, while the curriculum in mastering listening could be achieved by only 138 respondents (35%), while the goal of curriculum which was related to children's speech could reach only 166 respondents (42%). The results of this study showed that social isolation (learning from home) had a significant negative effect on learning to read and speak in children [48]. These data were confirmed by a study by Bao et al. [49] conducted on a sample of 3170 preschool children over a period of 100 days of social isolation caused by a pandemic, and the study also used the results of a longitudinal early childhood study conducted in 2010/11. These authors, comparing the two studies, found that reading and language-speaking skills during social isolation caused by the emergency situation due to the COVID-19 pandemic decreased by 67% compared to 2010/11. The study also showed that children's reading of books decreased by 10.5% during social isolation, and that one of the main causes of those changes was the inability of children to read aloud, as a result of which they could not learn speech and language properly. The authors of the study [49] found that, during the school closure period, reading books at home led to an improvement in achievement on language assessment tests by 40% compared to children who did not read books at home during this period. Children with whom parents read books regularly every day had a significantly higher percentage of improvement in reading ability, a 79% higher improvement compared to children whose parents did not read books on a daily basis. These data are in line with the results of Kuhveld et al. [50] who found that the average reading achievement of children from third to seventh grade during 2020 fell by 35%. Davies et al. [51] examined the language and cognitive abilities of 189 children aged 8 to 36 months. The study was done in the UK, and the results showed that the development of receptive vocabulary was better in younger children compared to older children. These authors also stated that more frequent visits of children to preschool were statistically significantly associated with a more pronounced receptive vocabulary, while children who went to preschool less often had

a significantly less developed receptive vocabulary. The results were confirmed by a survey of teachers [52] when most teachers expressed the opinion that children spent half as much time learning when schools were closed compared to the period before schools were closed due to the COVID-19 virus pandemic. The occurrence of the COVID-19 pandemic has opened a new question when it comes to the development of speech and language of children, and that is what and how much influence people outside the family can have on the development of speech and language. Kanero and Aktan [53] in their study, in which they assessed children's achievements in vocabulary assessment tasks done in Turkey on two occasions, at the beginning of isolation due to a pandemic and three weeks later, stated that due to limited children's interaction with people outside the family, children's speech might stagnate, but on the other hand, there might not be language development disorders, because early language development depends primarily on parental contributions, so social isolation should not have a significant negative impact on language development. The authors found that mothers contributed statistically significantly to the development of children's vocabulary during social isolation caused by the COVID-19 pandemic compared to fathers, who did not significantly contribute to speech development. According to WHO recommendations [31] on physical activity and behavior of preschool children of calendar age, each child should spend at least 180 minutes a day in some physical activity, not exposed to screening more than an hour a day, and have 10 to 13 hours of quality sleep (31). However, due to the COVID-19 pandemic, it is a great challenge for parents to follow these recommendations, and the main reason is the closure of preschool and school institutions and social isolation. In the literature, so far there has been very little data on what content the children filled their free time with and how they spent the same time during social

isolation. We have not found data on whether children spend less time during the day in physical activity, whether they stay awake longer, whether they sleep shorter, whether they spend most of their time exposed to screens, but it is known that non-compliance with these recommendations in early childhood can cause cognitive impairment, psychological disorders and disorders of mental functions of thinking, attention and memory, which can negatively affect the development of speech and language in preschool children (54). Also, it has been proven that children are less physically active and sleepy, with a less consistent sleep pattern on days that are not structured or on non-school days compared to school days (55). There is very little data in the literature on whether children spend less time with peers during social isolation, more time on computers or television, or spend most of their time playing with toys. Guan et al. (21) state that they interviewed 97 parents of preschool children in South Korea during the social isolation caused by the COVID-19 pandemic. In this study, it was found that 79 (91%) parents reported that the time spent by preschool children on television or computer screens during a pandemic increased significantly and 46 (94%) of 49 parents reported that children playing and playing sports decreased significantly.

Conclusion

The situation caused by the COVID-19 pandemic has led to numerous changes in dai-

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ly activities that have affected the development of children. The closure of preschools and schools has led to social and emotional problems for children, such as significantly fewer hours of sleep, poorer nutrition, more time spent on electronic devices, less physical activity, and the development of higher levels of stress. All this can significantly contribute to the damage to the physical and mental health of children, and consequently to disorders in the development of speech and language. Wearing protective masks, social distancing, and especially social isolation, as well as learning from home via electronic platforms has a large number of gaps that negatively affect the development of speech of preschool children, so this review can serve the Ministries of Education in the surrounding countries to precisely define models of learning from home through electronic platforms in such a way that learning is aligned with the characteristics of preschool children, so that children's speech and language skills during the COVID-19 pandemic can be improved. Finally, the limitation of this study is that there has not been much research addressing this topic that we could rely on in our review study. Future research should, therefore, be based on further consideration of this topic, as well as on the extent to which the accessibility of special educators and rehabilitators and therapies during the pandemic has affected children's speech and language development, and whether there are gender differences, sociodemographic characteristics, material status of parents and others.

Conflicts of interest. The authors declare no conflict of interest.

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Uticaj socijalne izolacije tokom pandemije COVID-19 na razvoj govora i jezika kod djece predškolskog uzrasta

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Govor je zvučni način komunikacije oblikovan ritmičkim jedinicama slogova, riječi i rečenice te je kao takav svojstven čovjeku, jedinom biću čiji su organi i psiha osposobljeni za ovaj proces. Usporenje razvoja govora se definiše kao pojava u kojoj dijete ne počinje sa govorom na vrijeme ili u obrascu govora postoje greške koje nisu primjerene u odnosu na dati kalendarski uzrast. Poznato je da su značajni faktori rizika za nastanak usporenja govora kod djece predškolskog uzrasta fizičke, a najčešće socijalno-emotivne prirode. Za normalan razvoj govora neophodno je da se dijete nalazi u ljudskom okruženju, pa zbog toga treba uvijek širiti krug osoba sa kojima djeca stupaju u kontakt.

Cilj ovog rada je da pregledom postojeće literature prikaže radove koji su ispitivali uticaj socijalne izolacije u toku pandemije COVID-19 na predškolsku djecu, te na razvoj govora i jezika kod djece predškolskog uzrasta.

Skoro nastala pandemija korona virusne infekcije (COVID-19) je dovela do toga da je većina zemalja svijeta uvela vanrednu situaciju, uvođenje karantina, zatvaranje javnih ustanova, a predškolske ustanove, vrtići i škole su zatvoreni u 172 zemlje. Ove epidemiološke mjere su dovele do socijalne izolacije i do pojave da djeca moraju da uče u kućnim uslovima, što se manifestovalo pojavom poteškoća u razvoju govora i jezika. Istraživanja su pokazala da su djeca za vrijeme pandemije u odnosu na period prije značajno više vremena provodila izložena televizijskim i kompjuterskim ekranima, a manje u igri i fizičkoj aktivnosti.

Ključne riječi: govor, razvoj govora, socijalna izolacija, pandemija COVID-19 virusa, djeca predškolskog uzrasta



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Review

Significance and assessment of emotional intelligence of nurses

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Summary

Emotional intelligence and health care are closely linked. Empathy is regarded as one of key dimensions of emotional intelligence. The nursing profession has numerous general, but also generic, competencies which requires not only technical knowledge, but also psychological support in everyday work. The aim of this review paper is to point out the importance of assessing the emotional intelligence of nurses on the basis of recent data from the literature. There are many challenges and various sufferings that many health workers are exposed to, especially nurses, which clearly indicates the necessary fact, ie. requires a high degree of emotional skills and competence, because the more complex the job, the more important emotional intelligence. High self-awareness, self-control, the ability to cope with feelings are just some of the competencies that nurses/ technicians should possess. All these characteristics are important factors of emotional intelligence and a basic prerequisite for providing empathy. There are numerous tests and instruments used to assess emotional intelligence.

Keywords: nurses, emotional intelligence, assessment, empathy, communication

Introduction

Emotional intelligence is a set of abilities to understand and manage many feelings on which behavior and the way decisions are made depend. There are seven types of intelligence, and one of them is emotional intelligence, intelligence that we can influence, unlike innate abilities such as cognitive intelligence [1, 2]. In nursing practice, an important component is emotional intelligence because emotions are an integral part of health care, which is a reflection of professionalism in nursing. Emotional problems are more pronounced in patients with incurable diseases, which requires an adequate, professional approach of nurses, because in this way, through a relationship built on trust, a comprehensive assessment of many symptoms can be realized and the physiological, psychological and social needs of patients can be met [3, 4]. For a successful cooperation with patients, nurses must have different skills of understanding, providing assistance, ability to resolve conflicts, but also to have an adequate way of communicating
and an empathic attitude, because empathy is the most important component of emotional intelligence to recognize and understand patients' feelings [5]. The aim of this review was to point out the importance and assessment of the emotional intelligence of nurses on the basis of data from recent literature.

The concept of emotional intelligence

Emotional intelligence additionally represents an experience for motivation, conceptualizing plans, appropriate decisions, stability, balance, resourcefulness and adaptability in achieving life goals, but emotional competences are basic abilities for processing and managing emotions. During 1980, emotional intelligence was equated to rational thinking given to us by genetics and we cannot have much influence on it, especially after fully maturing. In the 1980s, American psychologists established the theory of emotional intelligence, emphasizing that coping in different life situations had a greater effect on cold and objective data processing [6].

Howard Gardner, a psychologist, observed the so-called "multiple intelligence" model that best pointed out the difference between intelligence and emotional ability. It is necessary to distinguish between interpersonal intelligence in order to identify the feelings and intentions of others, and emotional intelligence which is the ability of self-control and implies the development of self-awareness, control and motivation. With the development of emotional intelligence, empathy and social skills are created in interpersonal relationships [7]. According to psychologist Daniel Goleman, emotional intelligence has five main elements and characteristics: empathy, motivation, self-control, self-awareness and social skills [8].

Cognitive and emotional intelligence are two different and mutually independent intelligences. Cognitive intelligence is innate, we cannot influence it, we cannot learn it or increase it. Emotional intelligence is not innate, so we can influence it, it can be learned and developed throughout life. The construct of emotional intelligence has been the focus of interest in recent decades, and it consists of two basic types of skills: self-management skills and successful cooperation skills with others. Both types of skills are important for success in business and the achievement of any person's life goals. The abilities that are most in demand on the labor market are: self-awareness, self-confidence and self-control, dedication and honesty, the ability to communicate and accept changes. This means that the most important factor is not a degree and expertise, especially in the nursing profession, but rather emotional intelligence [8].

Components of emotional intelligence in nursing practice

An integral part of nursing practice is understanding one's own emotions because understanding others depends on it. The high level of emotional intelligence of nurses increases patient satisfaction, because nurse is the first person who will best recognize the emotional reactions and all the difficulties that ail patients, and provide them with adequate health care, full support and assistance. As Florence Nightingale pointed out, it is necessary for nurses to have a high degree of emotional intelligence due to the holistic approach to patients. Florence Nightingale possessed a number of characteristics of emotional competence (understanding, desire to control emotions, energy, responsibility, self-confidence, ambition, empathy, etc.), which marks the beginning of development of nursing, with which emotionally competent nurses of today can identify with. Health care by definition is the complete care for someone, however it is not fulfilled, if the emotional aspects of the patient are not satisfied. Emotional intelligence is considered the key characteristic for success in nursing practice [9, 10].

Very important components of emotional intelligence are self-control and self-awareness, which affects the control and direction of emotions. Therefore, in nursing practice, an important prerequisite for maximum engagement for the patient's overall problems are emotionally intelligent nurses who are able to separate their own emotions from the patient's emotions and problems [11, 12].

The results of many relevant studies show that people with higher emotional intelligence are better prepared to identify early signs of undesirable behavior [13, 14]. The nursing profession has numerous general, but also generic, competencies which requires not only technical knowledge, but also psychological support in everyday work. There are many challenges and various sufferings that many health workers are exposed to, especially nurses, which clearly indicates the necessary fact, ie. a high degree of emotional skills and competence is required, because the more complex the job, the more important emotional intelligence is [15]. Empathy, as one of the more important aspects of emotional intelligence, is a central factor in many nursing theories that enable nurses to develop a therapeutic relationship with patients and their families, and to cope better with stress. Health care requires the nurse to continuously communicate with patients and other health care professionals. Today, health care includes not only high-quality medical care, but also the concept of care that encompasses the goals, priorities and patient's choices, including his/hers emotional, social and spiritual needs, using the power of interdisciplinary resources [16]. In addition, high empathy can have both positive and negative effects to the patient's medical care, depending on the degree of connection to other dimensions of emotional intelligence. Nurses with high self-control when dealing with criticism are more open in communicating with the patient, making them more likely to share their own worries and feelings with them. As a result, nurses better understand the patient, discuss his/her concerns, help him/her and show care with respect [17]. Such nurses nurture relationships based on trust and mutual understanding, develop positive relationships, and help the patient sustain each other's emotional changes. Care and full support cannot be limited only to physical help, the psychological and spiritual needs of the patient are vital. Therefore, the role of emotional intelligence in care should be viewed in two dimensions: understanding the patient's emotions and the competence of nurses to manage those emotions [18].

Empathy is a complex ability that allows individuals to understand and feel the emotional states of others as a result of compassionate behavior [19]. Empathy encompasses cognitive, emotional, moral and behavioral abilities due to understanding and timely response to other people's suffering. Empathy has many benefits, including better patient experiences, improved treatment outcomes, more frequent adherence recommendations, fewer mistakes in care and treatment, and greater satisfaction of health professionals. The philosopher Theodore Lipps expanded the concept of empathy, and believed that internal imitation and experiencing the actions of others led to the emergence of empathy [20]. Martin Buber pitted humanity and caring for others against objectification and dehumanization of others, and portrayed an empathic relationship as "I-Thou" instead of "I-It." Lack of empathy is possible among people, but such prejudices are common in health care institutions. It is important to eliminate discrimination (based on gender, race, nationality) and provide equal care to all patients. Medical professionals are obliged to conduct self-help and build their own emotional health in order to be able to help others and maintain the necessary level of empathy [19].

The communication skills of nurses are closely related to their emotional intelligence. Nurses with developed communication skills have a positive effect on the satisfaction of patients facing serious illnesses, improve the general well-being and influence the patient's experience. As an important component of communication, it is important to emphasize active listening, which is a prerequisite for positive interaction between two or more people. Through active listening, empathic understanding is emphasized, and interpersonal relationships are improved. It can be said that humanity is the main characteristic of health workers, and knowledge and experience are guides to work [21, 22, 23].

Assertiveness is the ability to express one's own opinion in a calm and positive way, without aggression or passive acceptance of someone else's opinion. To be assertive means to stand up for your rights, while expressing your thoughts, feelings and beliefs in an honest and appropriate way. Respect for other people's rights is an important segment of this skill, which leads to less harassment of others and yourself. Lack of assertiveness often leads to conflicts between people and such negative dialogue is considered an inappropriate way of interaction [24]. It is very important to be confident in yourself and your skills, and use self-confidence to achieve the desired result. Such approach does not entail domination because we must be aware at all times that we are part of a team. It is necessary to control body language and tone of voice, taking care to achieve a balance between passivity and aggression. It is important to listen to the other person in order to make a joint decision and achieve mutual benefit. It is important to be an active participant in the conversation and present the arguments in a clear and reasonable way [25].

Social intelligence is the ability to get along well with others that includes the ability to cooperate with each other. It also involves a certain amount of self-awareness about one's own perceptions and reactions, from which it can be concluded that it is related to emotional intelligence. Measuring social intelligence involves identifying key skills interactions, and assessing them through behavior. Social intelligence can be improved during life because it improves as you mature and gain experience in working with others. Some shortcomings in an individual's social intelligence stem from the inadequate development of the emotional segment, or vice versa, which points to the clear fact that continuous learning is needed to gain awareness and skills needed to succeed in social, business and professional situations [26].

Epidemiological research has concluded that emotional intelligence is a useful tool for all nurses, but especially nurses who are leaders of some teams because emotional intelligence contributes to the positive achievement of effective management in health care. The nature of the nursing profession itself is focused on health, promotion, disease prevention, and care for the physically and mentally ill and handicapped of all ages, [27] requiring nurses to be emotionally intelligent to respond to their diverse duties [27]. Numerous studies show that high levels of emotional intelligence are associated with a transformational model of leadership, as well as that emotionally intelligent management "drives" proactiveness, team empowerment, patient satisfaction with care, and well-being at work. Individuals have the ability to identify and experience a wide range of emotions in everyday life [28-33]. However, some of them are not able to use, understand and manage these emotions. This fact suggests that it is necessary to improve social and emotional skills. By searching and analyzing systematic reviews and meta-analyzes from three databases (Pubmed/Medline, EM-BASE, Scopus) where the works were obtained in which a larger number of examinees were included, it was concluded that by implementing social and emotional learning programs nurses could acquire the knowledge, attitudes and skills necessary for understanding and managing emotions, achieving positive goals, maintaining positive relationships and making responsible decisions in work [34, 35, 36, 37].

Measuring and assessing emotional intelligence in nurses

Recently, the importance of approaching the examination of emotional intelligence in nurses as the ability, ie tests that would require resolving numerous conflicts and finding solutions, has been emphasized. In the current practice of measuring individual differences in emotional intelligence, self-assessment methods (self-assessment of one's own abilities) and methods of measuring emotional intelligence as mental abilities by performance tests are most often used.

There are numerous scales for self-assessment of one's own ability to regulate emotions and moods that were conceived from Mayer-Salovey's model. The mentioned model indicates that reflective processes, evaluation and observation of one's moods indicate that a person pays attention to own feelings, ie is aware of them, which enables him/her to understand and regulate them, and thus to evaluate them [38]. The self-assessments derived from this model are intended to measure two complex levels of emotional intelligence, understanding and reflexive regulation of emotions: the State Meta-Mood Scale (examines current regulation abilities) [39] and the Trait Meta-Mood Scale (assesses long-term regulatory styles) [40].

State Meta-Mood Scale is the first scale to assess the elements of emotional intelligence and includes five factors about understanding and experiencing one's own moods (confusion, acceptance, typicality, and variability). The State Meta-Mood Scale include meta-evaluation and meta-regulation of moods. The range of responses ranges on a Likert-type scale from 1 (strongly disagree) to 5 (strongly agree) with a higher score indicating a better assessment of one's own moods and a greater ability to instantly regulate one's own moods. The internal consistency of the scale ranges from $\alpha = 0.75$ for the factor of mood acceptance to $\alpha = 0.80$ for the factor of influence of mood

on behavior and thinking. It can be said that the scales show a moderate association with empathy constructs and coping strategies. The authors clearly state that mood scales are measure of a condition rather than a trait, and emphasize different aspects of personality. The mood meta-regulation scale had three subscales called: correcting, maintaining, and calming the mood. The reliability of the internal consistency of the subscales ranged from $\alpha = 0.78$ for the mood maintenance factor, $\alpha =$ 0.79 for the mood calming factor, to $\alpha = .87$ for the mood correction factor. Meta-regulation scales have shown a significant association with stress management scales [40]. Because the scales described above were used mainly to assess current moods, the authors constructed the Trait Meta-Mood Scale (40) that was intended to assess relatively stable individual differences. Factor analysis of 48 particles (30 particles retained in the final version) resulted in three factors: an attention subscale measuring how much attention people pay to their emotions (Cronbach alpha α = .86), a clarity subscale measuring how clearly people understand their own moods (Cronbach alpha α = .86) and the correction subscale measuring the severity of the need to improve mood (Cronbach alpha α = .82) [41].

The instruments most commonly used to assess emotional-social competencies are the Bar-On Emotional Quotient Inventory (EQs) [42] and the Toronto Alexithymia Scale (TAS-20) [43]. The most famous scale for self - assessment of emotional - social competencies is Bar-On Emotional Quotient Inventory (EQs). The instrument is used to discover personal development, emotional intelligence, and emotional and social competencies. The range of responses ranges on a Likert-type scale from 1 (very rarely true for me or not true for me) to 5 (very often true for me or true for me) with a higher score indicating greater efficiency in emotional and social functioning. The higher the result, the more likely is the prediction of better functioning

in meeting everyday requirements and challenges. Bar-On publishes satisfactory data on questionnaire reliability coefficients (α = .69 to α = .86). A great advantage of the questionnaire is its high prognostic reliability for managerial positions and academic success, and it can also be used as a psychodiagnostic tool in research, diagnosis, selection and psychotherapeutic evaluations to assess emotional and social functioning [44].

The Toronto Alexithymia Scale (TAS-20) [43] consists of 20 items and is one of the most commonly used alexithymia measures. Alexithymia is defined as the inability to distinguish, name, and express emotion. The scale has three subscales: Difficulty Describing Feelings to measure difficulties in describing emotions, Difficulty Identifying Feelings to measure difficulties in recognizing emotions, and Externally-Oriented Thinking to measure the propensity of individuals to direct their concentration toward the outside environment. Claims are graded on a Likert-type scale (from 1 = strongly disagree to 5 = strongly agree). The total scale score is the sum of the responses to all 20 items, and the result for each subscale factor is the sum of the responses for that subscale. TAS-20 uses a precise score: equal to or less than 51 = not alexithymia, equal to or greater than 61 = alexithymia, and scores 52 to 60 = possible alexithymia. The scale shows good internal consistency (Cronbach's alpha = .81) [43].

The Emotional Competence Questionnaire (UEK-45) is most commonly used in Croatia [44]. UEK-45 is an abbreviated version of the UEK-136 Emotional Intelligence Questionnaire, built on the model of the author Takšić, since 1998 [45]. The questionnaire contains 45 items classified into three subscales: the ability to perceive and understand emotions (reliability of the scale from $\alpha = .82$ to $\alpha =$.88), the ability to express and name emotions (reliability of the scale from $\alpha = .78$ to $\alpha = .81$) and the ability to control emotions (reliability scale from $\alpha = .68$ to $\alpha = .72$). The range of an-

swers ranges on the Likert-type scale from 1 (does not apply to me at all) to 5 (fully applies to me). Emotional Competence Questionnaire scales assess emotional intelligence as a personality trait, but due to frequent complaints that intelligence can only be measured by ability tests, the author opted for the phrase "emotional competence". Here, the importance of the existence of emotional competencies in people's daily lives is emphasized, as the reason for the existence of emotional intelligence. The formation of the overall result is based on high correlations between subscales ranging from 0.35 to 0.51, and is expressed as a measure of general emotional competence (reliability from $\alpha = 0.87$ to $\alpha = 0.92$). The reliability of the whole Questionnaire in different samples ranges from $\alpha = 0.88$ to $\alpha = 0.92$ [45]. The prognostic reliability of UEK-45 was verified by correlations with the primary criteria for the construct of emotional intelligence: life satisfaction and various aspects of empathy, and one of the basic criteria of emotional intelligence is empathy. In the hierarchical regression analysis, a significant contribution of the Questionnaire scales to the explanation of the variance of life satisfaction was found; the best predictor of life satisfaction has been the emotion management scale [45].

The Emotion Regulation and Control Questionnaire (ERIK) [46] contains 20 items related to the regulation and control of negative emotions and moods. The goal is to assess the magnitude of (negative) effects of emotions and moods on thinking, memory and behavior, as well as the ability of emotional control. Factor analyses of the structure of ERIK show that there are three interpretable factors: the influence of emotions and moods on thinking (to examine the effect of emotions and moods on thinking and behavior, reliability α = 0.70), the influence of emotions and moods on memory (to measure emotional memory, reliability α = .70) and control of emotional reactions (for testing the ability of emotional control, reliability $\alpha = .60$). The range of responses ranges on the Likert-type scale from 1 (does not apply to me at all) to 5 (fully applies to me) with a higher score indicating a greater negative impact of emotions and moods on thinking and memory, and weaker regulation and control [46].

The first known test of emotional intelligence is the Multifactor Emotional Intelligence Scale (MEIS) [47], which includes 12 competency measures from the EI model located in four broad areas of ability: emotion perception, emotion assimilation, emotion comprehension and emotion management. The reliability of the scale ranges between $\alpha = 0.35$ and α = 0.94. The worst results were for the expert criterion (the method in which the expert determines the correct answer to the EI test), and the emotion management subscale proved to be the least reliable. Constructed tests are most often used in Croatia: Emotion analysis test [48] is intended to assess the dimension of understanding and analysis of emotions for 25 problems, and the task is to find the two most accurate and two least correct solutions in each problem, so the test has a total of 100 tasks. Its reliability is satisfactory (about $\alpha = 0.80$). The emotion vocabulary test [47] is the test in which the stimulus word is emphasized and six possible answers are suggested, of which only one is correct. The final version of the test contains 102 tasks, and satisfactory reliability was obtained on different samples (from α = 0.87 to α = 0.92).

Disadvantages of using tests to assess emotional intelligence in nurses

The biggest methodological problem with tests of emotional intelligence in nurses is identifying the correct answer. People in everyday life often determine the correct answer based on agreement with the rest of the examinees. According to the Mayer and Salovey's model, emotional knowledge is an integral component of the social context of communication and interaction, which allows determining the correct answer on tests based on agreement with the rest of the group (the consensus method). The main problem with the consensus method is the distribution of the obtained results, which shows a high asymmetry index, since most respondents are expected to choose the correct answer to each question. Normal distribution is a prerequisite for many statistical analyzes, and is also important because of the ability to distinguish between people with average and high abilities on tests. There are five consensus methods for determining the correct answer [47], and they are called proportion (mode, "extended" mode, and distance and standardized distance). The "extended" mode method and the distance method are only suitable for Likert-type scales. At a standardized distance, the results are transformed into z - values, and then the distance between the answer and the optimal answer is calculated. Another way is for the author to determine the correct answer, which is called the target method, and then there is the expert method in which an expert determines the correct answer to the test. The problem with the target method is that the author of the test may not be able to accurately express his/hers own emotions, ie he/she can only express positive or prosocial emotions, and with the expert method, there are no clearly defined criteria for determining who is the expert in emotional intelligence. It is interesting that different ways of scoring on the emotional intelligence test can give different results because there are many ways in which emotions can be experienced and interpreted, and such a way of scoring the test provides useful information about how a person reacted in comparison to how most people reacted to the situation [49, 50].

It is evident that the mentioned instruments used to assess emotional intelligence in nurses are in the form of a self-assessment scale, which can lead to distorted answers, the impossibility of timely assessment of how nurses behave in accordance with their beliefs about the level of their emotional intelligence ability, as well as not acceptance of conceptual answering by self-assessment because such answers are not acceptable for the assessment of mental ability.

Conclusion

Emotional intelligence encompasses various abilities, general and generic competencies that are necessary for quality nursing practice. Emotional intelligence provides numerous benefits not only to patients, but also to nurses, because emotionally competent nurses deal with their own emotions better, which leads to better work, and rarely leads to chronic fatigue and burnout at work. Whether emotional intelligence is part of mental abilities or seen as a way of behaving for adequate social behavior and emotion management, emotional intelligence is seen as a mandatory part of a common construct, which clearly indicates the need to continue developing of numerous theories and to associate them with contemporary theories of emotional personality development. Given the importance of nurses' emotional intelligence, its development should be a priority for every nurse.

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Značajnost i procjena emocionalne inteligencije medicinskih sestara

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Emocionalna inteligencija i zdravstvena njega usko su povezane. Empatija, kao dio emocionalne inteligencije, čini jedan od vrlo važnih segmenata emocionalne inteligencije. Sestrinska profesija posjeduje brojne opšte, ali i generičke kompetencije što zahtijeva ne samo tehničko znanje već i psihološku podršku u svakodnevnom radu. Cilj ovog preglednog rada je da se na osnovu novijih podataka iz literature ukaže na značajnost procjene emocionalne inteligencije medicinskih sestara. Brojni su izazovi i različite patnje kojima su izloženi brojni zdravstveni radnici, posebno medicinske sestre, što jasno ukazuje na potrebnu činjenicu, tj. potreban visok stepen emocionalnih vještina i kompetentnosti, jer što je posao složeniji, to je emocionalna inteligencija važnija. Visoka samosvijest, samokontrola, sposobnost nošenja s osjećajima, samo su neke od kompetencija koje bi medicinske sestre/tehničari trebalo da imaju. Sve te navedene osobine su važni faktori emocionalne inteligencije i osnovni preduslov za pružanje empatije. Brojni su testovi i instrumenti koji se koriste za procjenu emocionalne inteligencije.

Ključne riječi: medicinske sestre, emocionalna inteligencija, procjena, empatija, komunikacija

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The review paper consists of: Introduction, Relevant subheadings, Conclusion, References. The review paper must contain at least 5 papers by the author of the article from the narrow field from which the paper is from.

Patient or case reports consist of: Introduction (Aim of the paper should be stated as the last paragraph of the Introduction), Patient report, Discussion, References. For other types of papers, the abstract does not have a special structure.

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The papers should be prepared in accordance with the Vancouver agreement (V Edition, review from 1997), initiated by the International Committee of Medical Journals Editors. *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*: <u>www.icmje.org</u> – <u>http://www.icmje.org/urm_full.pdf</u>

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On a separate page, type the title of the paper, full names and surnames of the authors, names of institutions, abstract and keywords in English, if the paper is written in Serbian. (For papers written in English, in addition to short summary in English, short summary in Serbian is also required).

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Chapter in a book:

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Book:

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Article from a congress or meeting:

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Dissertation:

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Journal article in an electronic format:

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Web page on the Internet:

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