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HOLISTIC APPROACH TO AGE-RELATED RESTRUCTURING OF THE IMMUNE SYSTEM (QUEST FOR INTEGRATIVE MEDICINE)

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Ancient evolutionary involution of thymus in vertebrates is the only physiologic process that shows marked changes in the aging body. Due to thymic involution, immunosenescence is characterized by progressive dysfunction of the adaptive type of immunity mediated by lymphocytes, accompanied by increased activity of the innate type of immunity mediated primarily by macrophages. In the elderly, development of age associated diseases represent a dynamic evolutive stochastic non-linear process resulting in various physiologic states, which at the same time are predictors of increased multimorbidity and grave infections. Transition from dynamic homeostasis to chaotic behavior can be provoked by bias in cellular interactions and long lasting imbalanced secretion of proinflammatory or anti-inflammatory chemokines. Whether or not some of the aberrant intra- and or intercellular homeostatic mechanisms in the immune system could propagate pathogenetic events in various clinical manifestations can only be expressed by probability, which depends on the genetic, evolutionary, environmental, epigenetic, and lifestyle factors.

Key words: thymus involution, immunosenescence, immune system remodeling, macrophages, innate immunity upregulation

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PROLOGUE

Nothing in biology makes sense except in the light of evolution (Theodosius Dobhzansky, 1973)

Genetic and behavioral variabilities (biodiversity of algorithms) of *Homo sapiens* based on Ch. Darwin and A. R. Wallace co-developers of the theory of evolution, are functionally regulated, coordinated and balanced by complex interactions at the intracellular level (among molecules), intercellular level (among cells), organ level (among organs), integrated at the level of the whole body (biological individuality), and in addition deeply influenced at the environmental level (various social and cultural elements), created by natural evolution over millions of years.

INDIVIDUALITY OF THE IMMUNE SYSTEM

The immune system is creation of evolution. It has arisen by exploitation of error nucleotide replication and it is more infallible than any other aspect of biological functions. (Macfarlane Burnet, 1972)

The brain and the immune system establish individuality at two levels: they help us adapt to life and so preserve us, and they make a record of what has happened. (Irud Cohen, 2000)

There are three ways in which information about past is archived in such a way that it can be used to improve future chances of survival. These are the immune system, the nervous system, and culture. (Richard Dawkins, 2013)

The immune system is one of the most important integrative multicellular systems in the body, which by continuous communications, interactions and balanced coordination with neural, endocrine and metabolic systems records, protects, creates and defines our individuality. The immune system as a sensory organ actively participates in maintaining body homeostasis by protection 1) against external hazards (infections by bacteria, viruses, parasites, and allergens), 2) against internal hazards (anti-self-reactivity and surveillance against tumors), and 3) by active participation in the pathogenesis of practically all diseases.

EVOLUTION OF THE IMMUNE SYSTEM

...no biological problem is solved until both the proximate and evolutionary causation has been elucidated... (Ernst Mayr, 1982)

From the evolutionary aspect, there are two types of immunity, innate and adaptive immunity.

Innate type of immunity
It is the phylogenetically oldest conserved protection mechanism against pathogens in animal kingdom, mediated by macrophages. Macrophages are strategically distributed in all tissues and organs, where they signal immediate potent nonspecific process of phagocytosis *via* TOL-like receptors, ingest and eliminate microbes, dead cells and/or their debris, and by additional activation modulate their dynamic relationship mutually interacting in secretion of pro-inflammatory and/or anti-inflammatory (protective) set of chemokines.

A***daptive type of immunity***
It is a phylogenetically younger, thymus dependent protective mechanism, with basic structure of Th-1 and Th-2 lymphocyte populations secreting pro-inflammatory and/or anti-inflammatory cytokines, which display extremely diverse repertoire of antigen-specific recognition receptors for identification and elimination of pathogens.

Thymus involution
Biohistorically, progressive thymic involution is the only physiologic process that shows marked changes in the aging body, representing an ancient and conserved evolutionary process in all vertebrates.

Immunosenescence
Due to thymic structural and functional involution, developing immunosenescence represents a complex process of recapitulation of inversely evolutionary pattern of the immune system.

Remodeling of the immune system is defined by two basic coexisting cellular processes, i.e. progressive functional dysfunctions of the younger adaptive type of immunity and domination of the innate type of immunity mediated by macrophages. In aged individuals, the process of thymic involution leads to modification and modulation of the immune system making the system more adapted to cope with pathogens in local environment. From the evolutionary perspective, structural and functional changes of the immune system in aged individuals represent optimization of resources of the aging body.

INTEGRITY OF THE IMMUNE SYSTEM

The harmonious cooperation of all beings arose not from the orders of a superior authority external to them but from them, a fact that they were all parts in hierarchy of whole formatting a cosmic pattern and what they obeyed were internal dictates of their own natures. (Chuang Tze, 3rd century BC)

The immune system consists of a huge number of individual immunocompetent cells penetrating most tissues/organs in the body, which continuously receive and transmit a great variety of excitatory and/or inhibitory signals creating a dynamic network responsible for control of basic reactivity and enhancement of effectiveness of the system in performing complex physiologic functions *via* permanent activities mediated by various humoral and cellular mechanisms.

Therefore, long lasting duration of imbalanced secretion of a number of proinflammatory and/or anti-inflammatory cytokines/chemokines with their pleiotropy, redundancy, synergistic and/or antagonistic activities and parallelism can act together with bias of cellular interactions. Human beings are maintained in dynamic stationary state as a thermodynamically open system with self-organization, complexity and emergence of new order characterized by a high level of adaptation. The complex behavior of the immune system emerges spontaneously from their structure with new properties that are not simple sum of individual units. The greater basic complexity, together with better adaptability to daily perturbations, is responsible for the remarkable stability of the system.

REACTIVITY OF THE IMMUNE SYSTEM

Everything in immune phenomena is soft-edged. There is not clear absolute whether or not a given reaction occurs when cell meets antigen can be only expressed as a probability whose magnitude depends on factors... as complex at cellular level as genetic and ecological factors which determine the course of evolution on macro level. (Sir Macfarlane Burnet, 1972)

Induced by an antigen (external or internal), the immune reaction represents a series of strictly locally and timely controlled cellular events in immunocompetent cells (APC, T and B lymphocytes) located in various tissues/organs, accompanied by balanced secretion of a number cytokines expressing various functional activities. Cytokines create the most important dynamic homeostatic network of the immune system, which is composed of a number of small glycoprotein molecules secreted by two different T-lymphocyte populations that interact in a non-linear fashion.

Two basic coexisting homeostatic mechanisms are responsible for dynamic homeostasis of the immune system, i.e. linear temporal oscillation mechanism regulated by negative feedback loop (dose response) and non-linear temporal mechanism responsible for dynamic modulations (positive feedback loop) when small changes in initial conditions (various types of physical and/or psychologic stresses) can provoke exponential non-anticipated abrupt effects in the full range of the system reaction (chaotic behavior, hypercytokinemia, cytokine storm) as one of the most important features of the cytokine network.

Coexistence of two homeostatic mechanisms and their bidirectional communications with fine tuning in secretion of various cytokine profiles represent one of the most important mechanisms that, in turn, orchestrate many vital functions responsible for longevity.

AGE-ASSOCIATED DISRUPTION OF THE IMMUNE SYSTEM HOMEOSTASIS

Indeed, regulation in the organism is a central problem of physiology. (Walter Cannon, 1929)

Multiple dysfunctions of the immune system (chaotic behavior*)* could be clinically manifested by general inflammatory reaction accompanied by multiple organ dysfunctions (systemic explosion) or compensatory anti-inflammatory reaction syndrome with severe immunosuppression (systemic inplosion). Pleiotropy, redundancy, synergistic and/or antagonistic activities and parallelism can act together with bias of cellular interactions. Human beings are maintained in a dynamic stationary state as thermodynamically open system with self-organization, complexity and emergence of new order characterized by high level of adaptation.

At the clinical level, it is deeply influenced by initiation, course, gravity, and outcome of a variety of clinical manifestations primarily by increased susceptibility to infections. Taking together, trivial degrees of built-in changes, by activation of non-linear type of control mechanism can significantly contribute to clinically good or poor prognosis.

Age related decline of adaptive type of immunity

Due to physiologic thymic involution, immunosenescence is functionally characterized by quantitative reduction of naive T-cell compartment, impaired immune response to newly pathogens and vaccination, exhaustion of some T-cell clones, and reduction of T-cell receptor diversity. Thus, various age-dependent subtle genetic defects could be responsible for irregular functional maturation of common lymphoid progenitors into T-cells as central effector and regulatory cells in the immune system. Consequently, by continuous exposure to various new antigens as a result of repeated clinical and subclinical infections, memory and differentiated effector T-lymphocytes with exhausted mitotic activity, continuously selectively accumulate in the immune space/tissues.

Age related chronic low-grade inflammatory syndrome (inflamm-aging)

Aging is associated with chronic low grade inflammation called inflamm-aging. (Claudio (Franceschi, 2000)

It is tempting to suggest that inflamm-aging might be considered to be the essence of life. (Tamas Fulop, 2018)

Highly heterogeneous monocytes/macrophages with great genetic potential and ability to rapidly change their biologic activities in response to local microenvironmental signals by their power of initiation and resolution of the immune reaction play a dominant role in development and propagation of chronic inflammation in aging population. The major cause of age-associated chronic inflammation is the ability of three distinct pattern types of microbe antigen receptors (PRRs) on macrophage surface to recognize and accumulate misplaced and misfolded self-molecules from damaged cells and cell debris (wearing out process). The process of recognition elicits low grade of subclinical inflammation *via* intra-cellular pathways by excess secretion of proinflammatory cytokines IL-6, IL-1, IL-8, TNF alpha, INF alpha and beta, together with upregulation of clotting factors and CRP, along with the prevalence of myeloid over lymphoid lineages (phagocytosis) in peripheral blood and loss of self-tolerance with production of autoantibodies. Multifunctional monocyte/macrophage lineage cells, found in nearly all tissues in the body, can be additionally gradually polarized into one of two functionally distinctive subsets, i.e. M-1 subset with increased production of proinflammatory chemokines and/or M-2 subset with increased production of chemokines which promote resolution of chronic inflammation (tissue repair).

Depending on initial conditions, variable relationship between M-1 and M-2 macrophage subsets in combination with imbalance in their dynamic mutual bidirectional communications, the M-1/M-2 system can be either dynamically stable showing oscillatory character (clinical remissions) or dynamically unstable showing progressive aggravation and/or relapses of various autoimmune and inflammatory diseases.

PUBLIC HEALTH SIGNIFICANCE

The deleterious impact of age on functional integrity of the immune system was not discovered until the average of human life expectancy was approximately in the range of 40 years. However, paradoxically, over the last 150 years, in spite of decreased body complexity and declining functions of the immune system, in the second part of longevity, human life expectancy resulted in dramatic increase to the unexpected average of above 80 years.

Age-associated diseases

The state of health or disease are expressions of the success or failure experienced by the organism in its efforts to response adaptively to environmental challenges. (René Dubos, 1965)

Development of age-associated diseases is a dynamic evolutive stochastic non-linear process which can in elderly patients result in various physiologic states and diversification of their clinical phenotypes. These various physiologic states are at the same time predictors of increased morbidity, physical disability, and mortality risk rate, which is frequently clinically accompanied by multimorbidity and grave infections. In elderly patients, transition from dynamic homeostasis into chaotic behavior can be provoked by bias of cellular interactions, imbalanced secretion of different proinflammatory and/or anti-inflammatory cytokines/chemokines caused by reduced body complexity clinically manifested as premature aging, chronic recurrent infections, immunodeficiency, autoimmunity, and cancer. As a consequence, age-associated low-grade chronic inflammation represents unsolved, uncontrolled and prolonged complex cellular events with detrimental effects on health by exacerbating biologic aging and development of different age related diseases.

Thus, inflamm-aging significantly contributes to worse course of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, atherosclerosis, dementia with cognitive decline, and metabolic disorders such as visceral obesity, fatty liver, diabetes type 2, and insulin resistance.

However, whether or not aberrant intracellular or intercellular homeostatic mechanisms alone or in combination with other homeostatic interactive communications among different macrophage subsets could propagate pathogenic event(s) in direction of any of clinical entities can be expressed only as a probability depending on different mutually interrelating conditions such as **evolutionary factors** *via* variable dynamics in progression rate of physiologic involution of thymus as an ancient conserved evolutionary process in all vertebrates taking place in the second part of longevity; **genetic factors** *via* polymorphism in regulatory genes (genetic coding variants) or structural changes in affected genes by built-in restrictions of genetic programs controlling and regulating different cellular processes.

Possible consequences of these genetic events could be manifested both at the intracellular level (restrictions of various degrees of different functional programs) and intercellular level (aberrant cell dialog which might result in profound dysfunctions of various homeostatic mechanisms), such as **environmental factors** *via* disproportion between persistent antigen load and/or duration of antigenic stimulation and the capacity of homeostatic immunoregulatory mechanisms; **immune factors** *via* developing age dependent immunodeficiency in elderly population related to gradually evolving selective restriction of various genetically controlled mechanisms in the thymus microenvironment; **neuro(psycho)-endocrine-immune factors** *via* unpredictable acute grave stress and/or repeated chronic stress could also be essential for disruption of dynamic homeostasis of the immune system and transition to chaotic behavior; and finally **epigenetic factors** *via* standing at the interface of the assumed disease risk gene and environmental exposure with profound effects on developmental cell plasticity, by activating specific hypothetical disease phenotype, particularly in case of developing and aging cells.

Namely, the epigenome is a molecular code superimposed upon genome that controls how genes are turned on and off without altering the underlying DNA sequence, which in turn, may change due to an adverse environment(s) into various active disease phenotypes. All the mentioned factors can additionally contribute to genomic instability, especially in the second part of lifespan, by decreased repair capacity and cumulative damage to DNA molecules, by modification of subcellular structures that may alter gene expression patterns, by oxidative damage to vital macromolecules, and by telomere shortening in replicative cells responsible for functional decline in different tissues and organs.

INSTEAD OF CONCLUSION

Aging is a journey along the road of stochastic evolutive aging creating immunodeficiency syndrome process resembling the ***SCILLA and HARIBDA MYTH,*** when escaping one trap, one can drop in another.

POST SCRIPTUM

In contrast to genetic changes, the reversible nature of epigenetic mechanisms makes these pathways promising venues in the development of regimens against age related decline and disease (epigenetic environmental factors beneficially influencing functional activities of the immune system in aging populations) such as **public health factors** by advances in medical sciences, improved nutrition, massive vaccination, rational use of antibiotics, environmental justice and equity, improved socio-economic conditions and health care accessibility, **lifestyle factors** by modified various and specific social, historical and cultural influences in combination with compassionate health care, mindfulness, physical activity, and finally by introducing **holistic approach** in the treatment of patients including whole person body, mind and spirit (personalized medicine).

EPICRISIS

General practitioner must be primarily social worker and teacher. *(Andrija* Štampar*, creator of social medicine in Croatia, 1925)*

Historical experience together with epidemiological, clinical and laboratory studies collected in the last 150 years has already reflected in the visionary definition of health accepted by Constitution of the World Health Organization and Economic and Social Council of the United Nations, New York in 1946, by declaring that ***HEALTH IS A STATE OF COMPLETE PHYSICAL, MENTAL AND SOCIAL WELL-BEING AND NOT MERELY THE ABSENCE OF DISEASE OR INFIRMITY.***

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SAŽETAK

HOLISTIČKI PRISTUP PROCESU RESTRUKTURIRANJA IMUNOSNOG SUSTAVA U STARIJOJ DOBI (POTREBA ZA INTEGRATIVNOM MEDICINOM)

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Involucija timusa je evolucijski vrlo star i jedinstven fiziološki proces u svih kralježnjaka. Proces je intimno povezan s remodeliranjem imunosnog sustava u kojem dolazi do selektivnog slabljenja sustava adaptivne imunosti posredovane limfocitima te dominacije evolucijski starijeg sustava urođene imunosti posredovane primarno makrofazima. U starijoj populaciji dolazi do disbalansa dinamičke homeostaze zbog nedostatne komunikacije između stanica imunosnog sustava i neuravnoteženog lučenja proupalnih i protuupalnih citokina kemokina. Hoće li neke od produženih i neuravnoteženih interakcija imunosno kompetentnih stanica imati određene kliničke manifestacije u velikoj mjeri ovisi o genetskim, evolucijskim, okolišnim, epigenetskim i kulturološkim čimbenicima.

Ključne riječi: **involucija timusa, remodeliranje imunosnog sustava, urođena imunost, makrofazi, imunosenescencija**

MORPHOMETRIC ANALYSIS OF VASCULAR CLEFTS IN CHILDREN WITH SYMPTOMS OF ACUTE APPENDICITIS AND NEGATIVE APPENDECTOMY

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Objective: Many cases of clinically suspected acute appendicitis show no microscopic signs of acute inflammation. Negative appendectomy rates differ greatly, partly due to various criteria used by different institutions to define acute appendicitis. In our practice, we have noticed that many of the negative appendectomy specimens contain prominent vascular clefts. The objective of this study was to determine the possible significance of vascular clefts, which has not been investigated yet. Our hypothesis was that vascular clefts are early, as yet unrecognized signs of acute appendicitis. ***Methods:*** We conducted a retrospective study by searching for patients who had negative appendectomy at the Zagreb Children's Hospital (2014-2019). There were 151 patients aged 1-18 years, 124 of which were included in the study group and 27 in the control group. Vascular clefts, if present, were measured microscopically. Statistical analysis was performed using Kolmogorov-Smirnov, Kruskal-Wallis, Mann Whitney, $\chi 2$ and Spearman's rank correlation tests. The level of statistical significance was set at $p<0.05$. ***Results:*** Out of the 124 patients included in the study group, 50.8% were female (n=63) and 49.2% were male (n=61). Mean age of the patients was 11.5 years and median 12 years. Negative appendectomy specimens showed prominent vascular clefts in 94 of 124 (75.8%) study group patients. Vascular cleft width varied between 140 and 1751 μm. Twelve (9.7%) specimens showed no signs of vascular clefts, and 18 specimens had partial vascular clefts that did not penetrate muscular wall of the appendix and consequently could not be measured. We also showed that there was a statistically significant difference between the number of appendices that contained fecaliths in their lumina in the study group as compared to the control group ($p<0.01$). ***Discussion:*** Negative appendectomies are still a problem in the 21st century medical practice. Although many cases of clinically suspected acute appendicitis microscopically show no signs of inflammation, in some cases symptoms may regress after appendectomy has been performed, even if there are no histopathologic signs of inflammation. In everyday practice, we noticed that in cases of acute suppurative or phlegmonous appendicitis, a dense inflammatory infiltrate is often seen passing through prominent vascular clefts, which we define as fissures of the muscular layer of the bowel (or in this case appendiceal) wall through which blood vessels and peripheral nerve branches pass on their way to and from the bowel. We tried to determine the possible significance of these vascular clefts. We collected 124 negative appendectomy specimens from the archives of our Department of Pathology and Cytology, all of which were removed from pediatric patients at the Zagreb Children's Hospital due to clinically suspected acute appendicitis. None of the 124 appendices met our criteria for acute appendicitis. We found that 94 of 124 (75.8%) negative appendectomy specimens showed vascular clefts. We also calculated the Zagreb Children's Hospital negative appendectomy rate during the 5-year period, which was 9%. ***Conclusion:*** Our results show that prominent vascular clefts in the muscular layer of the appendiceal wall are frequently found in negative appendectomy specimens. These clefts could be implicated in the pathophysiology of acute appendicitis and might be one of the first signs of acute appendicitis.

Key words: appendix, appendicitis, vascular cleft, negative appendectomy rate

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INTRODUCTION

Appendectomy is one of the most common emergency surgical procedures (1). However, in many cases of clinically suspected acute appendicitis, resected appendectomy specimens show no signs of inflammation. Negative appendectomy rate (NAR) is a quality metric used in the management of acute appendicitis, which determines the frequency of nontherapeutic appendectomies (1,2). NAR varies broadly in the literature from 1% to 40% (1). It is important to emphasize that NAR is also determined by definition of negative appendectomy (3). There are different criteria to define appendicitis and negative appendectomy (3). The most common definition of negative appendectomy is the absence of inflammation or pathology in the appendix, although some use stricter criteria such as absence of intramural neutrophils in the appendix (3). High NAR has been justified by some because there is a belief that the morbidity associated with negative appendectomies is not severe enough compared to the risk of developing appendiceal perforation (2). NAR has been in decline over the past decade, which can be attributed to better diagnostics, and some authors ascribe it to the increased use of ultrasound and computed tomography (CT) scans (2). However, what if the appendices that appear normal on histologic slides actually show early signs of appendicitis of which we are not yet aware? One study found evidence for an inflammatory pathologic condition at the molecular level in a histologically normal appearing appendix (4). Some suggest neurogenic appendicitis to be a possible causative mechanism of pain, especially in children. Cases such as these could theoretically explain the improvement of clinical symptoms after negative appendectomy (5). We conducted a retrospective study on negative appendectomy specimens focusing on the presence or absence of vascular clefts on histologic hematoxylin and eosin (H&E) stained slides. Vascular clefts are fissures of the muscular layer of the bowel wall through which blood vessels and peripheral nerve branches pass on their way to and from the bowel (Figure 1).

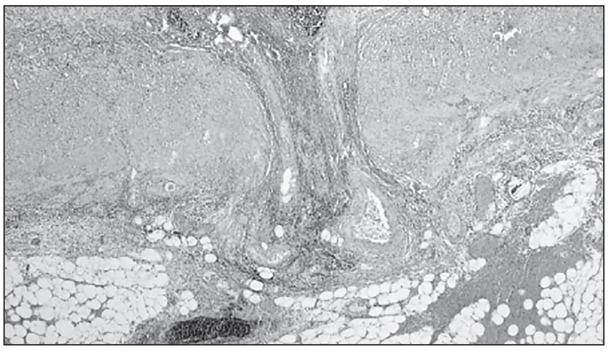

Fig. 1. *Vascular cleft with inflammatory infiltrate penetrating the muscular layer of the appendix.*

OBJECTIVE

The objective of this study was to determine the prevalence of prominent vascular clefts in negative appendectomy specimens, measure their width, determine whether there are fecaliths present in appendiceal lumina, and compare the findings to the specimens from the control group. Our hypothesis was that vascular clefts are early, as yet unrecognized signs of acute appendicitis.

MATERIAL AND METHODS

A retrospective review was conducted on patients having undergone appendectomy at the Zagreb Children's Hospital between January 1, 2014 and March 31, 2019. Patients were identified by searching through pathologic records of Department of Pathology and Cytology, Sestre milosrdnice University Hospital Centre. All resected appendices were serially sectioned and submitted to histologic analysis in their entirety. They were cut by microtome in multiple 3-5 μm thick sections. At our institution, acute appendicitis is histologically defined by the presence of neutrophils in the muscular layer of the appendix, and all other cases were considered to be negative appendectomies and were included in the study. Microscopic slides were retrieved and re-examined to determine the presence or absence of vascular clefts. We measured the width of vascular clefts at their point of entry through the muscular wall microscopically using the Olympus camera (Figure 2). If more than one cleft were found in the specimen, the widest cleft was measured and subjected to statistical analysis. The study included 151 patients aged 1-18 years. Out of these 151 patients, 124 were assigned to the study group. These patients showed clinical signs of acute appendicitis and were treated operatively as such; however, histology did not confirm the diagnosis of acute appendicitis. The remaining 27 patients were assigned to the control group. Their appendices were removed during abdominal surgery for non-related reasons as a precautionary measure. Statistical analysis was performed using Kolmogorov-Smirnov, Kruskal-Wallis, Mann Whitney, χ^2 and Spearman's rank correlation tests. The level of statistical significance was set at $p<0.05$. The analysis was made using GraphPad Prism version 8.0.0.

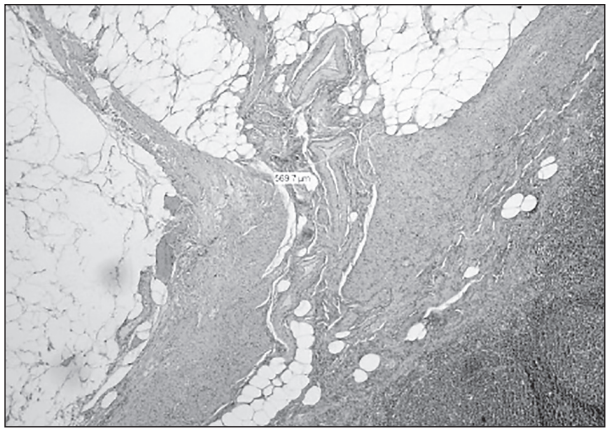

Fig. 2. *The width of the vascular cleft was measured at its point of entry through the muscular wall using the Olympus camera.*

RESULTS

A total of 1376 appendectomies due to the symptoms of acute appendicitis were performed at the Zagreb Children's Hospital during the 5-year period (from January 1, 2014 to March 31, 2019). Out of these 1376 appendectomy specimens, 124 showed no signs of inflammation, which means that the negative appendectomy rate (NAR) for the study period at the aforementioned institution was 9%. Out of the 124 patients included in the study group, 50.8% (n=63) were female and 49.2% (n=61) were male. Mean age of patients in the study group was 11.5 years and median 12 years. Ninety-four of 124 (75.8%) negative appendectomy specimens showed prominent vascular clefts. Vascular cleft width varied between 140 and 1751 μm. Twelve (9.7%) specimens showed no signs of vascular clefts, and 18 (14.5%) specimens had partial vascular clefts that did not penetrate muscular wall of the appendix on the sections analyzed and therefore were not measured. Out of the 27 patients included in the control group, 44.4% (n=12) were female and 55.6% (n=15) were male. Mean age of patients in the control group was 8 years and median 9 years. Nineteen of 27 (70.4%) control group specimens showed prominent vascular clefts. Vascular cleft width varied between 168 and 864 μm. Eight (29.6%) specimens had partial vascular clefts that did not penetrate muscular wall on the sections analyzed. The mean cleft size was larger in the study group than in the control group (363.72 *vs*. 301.75 μm), however, statistical analysis did not yield significant p values (p=0.36). We think this was the result of a relatively small control group. In the study group, 63.7% (n=79) of appendices contained fecaliths in their lumina as compared with 25% in the control group (p<0.01). The presence of fecaliths did not affect cleft size in the study group (337.41 μm with fecalith present *vs*. 410.10 μm with no fecalith, p=0.20).

DISCUSSION

The pathogenesis of appendicitis is still poorly understood (6,7). Commonly accepted theories are based on pathophysiologic changes caused by luminal obstruction, such as continued mucosal secretion and inflammatory exudation increasing intraluminal pressure and consequential obstruction of lymphatic drainage, edema and mucosal ulceration, venous obstruction, and finally ischemic necrosis (8-10). Even though appendicitis can be caused by direct luminal obstruction induced by fecaliths, lymphoid hyperplasia, impacted stool or rarely by an appendiceal neoplasm, according to recent theories these do not seem to be regular occurrences (5,6). The full spectrum of causes of appendicitis is not known yet, and some theories focus on genetic and environmental factors and infections (5). The lifetime incidence of acute appendicitis is 8.6% for men and 6.7% for women, but the incidence of appendectomy carried out for different reasons is 12% for men and 25% for women (9). The incidence of acute appendicitis roughly follows the development of lymphoid tissue, with the highest incidence in late teens and twenties (7,11,12). An accurate preoperative diagnosis of acute appendicitis is difficult and clinical assessment remains crucial in the management of suspected acute appendicitis (11,13). The typical presentation of acute appendicitis includes periumbilical pain, nausea, vomiting, loss of appetite, low fever, and malaise. Within 6-18 hours, the pain localizes in the right lower quadrant with associated guarding and rebound tenderness (11). About 20%-33% of patients present with atypical findings (11). Acute appendicitis requires early surgical intervention since appendiceal rupture causes significant rise in morbidity and mortality. Trying to reduce the risk of perforation by lowering the threshold for surgical intervention has led to a high NAR (11,13). NARs are higher in women of childbearing age (11). The reported complication rate following negative appendectomies is 6.1% (11). Negative appendectomies impose high cost to the patient and the healthcare system. CT scans and diagnostic laparoscopy should be only used in selected cases (11). The gross pathology and histology of acute appendicitis are quite variable. The outer appearance may not correspond to the degree of inflammation found on histologic slides (13). Acute suppurative or phlegmonous appendicitis is defined as neutrophilic inflammation of the appendiceal wall. Diagnostic criteria for acute appendicitis are controversial, as some believe that mucosal neutrophilic infiltration with superficial ulceration can be considered as an early criterion for acute appendicitis, whereas others require the presence of neutrophilic infiltration of muscularis propria (13). Since fecaliths and enteric infections can also cause superficial ulceration and mucosal inflammation (13), and as some studies suggest that mucosal inflamma-

tion of the appendix is not related to the symptoms of appendicitis (14), we considered the presence of neutrophils in muscularis propria to be the proper histologic criterion for the diagnosis of acute appendicitis. Negative appendectomy specimens in some cases have shown nonspecific changes such as cytokine elevation or neurogenous hyperplasia, which some believe may be the cause of clinical symptoms (13). However, to our knowledge, no one has yet investigated clinical significance of vascular clefts and their possible role in the pathogenesis of acute appendicitis. We searched the PubMed database using keywords such as "vascular clefts" and "appendix" or "appendicitis" in search for studies focused on or mentioning vascular clefts. We found an article describing widened vascular clefts as sites of weakness in the muscular layer of the appendiceal wall with a potential of developing appendiceal diverticula (14). No other mention of vascular clefts of appendiceal wall has been found.

In our study, we demonstrated that most (75.8%) of the negative appendectomy specimens contained prominent vascular clefts. Even though the mean cleft size was larger in the study group than in the control group, statistical analysis did not yield significant p values. This might be the result of a relatively small control group, which was a shortcoming of the study based on pediatric population. It is quite difficult to obtain healthy controls for comparison since all the specimens allocated to the so-called control group had been removed during surgery due to acute abdominal symptoms. This was the major limitation of our study. However, it may be possible to determine clinical significance of the presence and/or width of vascular clefts by comparing them to the severity of clinical symptoms or inflammation parameters (white blood cell count, C-reactive protein, etc.). We also showed that there was a statistically significant difference between the number of appendices that contained fecaliths in their lumina in the study group as compared with the control group ($p<0.01$). This finding is in line with the traditionally accepted theories about the pathophysiologic changes caused by luminal obstruction, which in this case might be connected to the development of vascular clefts and symptoms of appendicitis, even though the presence of fecaliths did not affect cleft size in the study group. The NAR calculated for the Zagreb Children's Hospital during the 5-year period (from January 1, 2014 to March 31, 2019) was 9%, which did not differ significantly from the NARs calculated at other institutions.

CONCLUSION

Our study demonstrated that prominent vascular clefts were present in most (75.8%) of the negative appendectomy specimens. Due to difficulties in obtaining control group specimens, we could not prove a statistically significant difference in vascular clefts between the study group and control group, but there was a statistically significant difference between the number of appendices containing fecaliths in the study group as compared with the control group. The possibility remains that vascular clefts might be one of the early signs of acute appendicitis. Further investigation is needed.

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SAŽETAK

MORFOMETRIJSKA ANALIZA VASKULARNIH KLEFTOVA U DJECE SA SIMPTOMIMA AKUTNOG APENDICITISA I NEGATIVNOM APENDEKTOMIJOM

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Cilj: Mnogi slučajevi klinički dijagnosticiranih akutnih apendicitisa ne pokazuju znakove akutne upale. Stopa negativnih apendektomija znatno varira, dijelom i zbog različitih kriterija koje razne institucije primjenjuju u definiciji akutnog apendicitisa. U našoj svakodnevnoj praksi primijetili smo da mnogi od uzoraka negativnih apendektomija sadrže izražene vaskularne kleftove. Cilj ove studije bio je odrediti moguće značenje vaskularnih kleftova koje nitko dosad nije istražio. Naša hipoteza je bila da su vaskularni kleftovi rani, dosad neprepoznati znakovi akutnog apendicitisa. ***Metode:*** Proveli smo retrospektivnu studiju tražeći bolesnike s negativnom apendektomijom u Klinici za dječje bolesti Zagreb (2014.-2019.). Pronašli smo 151 bolesnika u dobi 1-18 godina, od kojih smo 124 uključili u istraživanu, a 27 u kontrolnu skupinu. Vaskularne kleftove smo mjerili mikroskopski. Učinjena je statistička analiza pomoću Kolmogorov-Smirnovljeva, Kruskal-Wallisova, Mann Whitneyeva, $\chi 2$ i Spearmanova rank korelacijskog testa. Razina statističke značajnosti utvrđena je na $p<0,05$. ***Rezultati:*** Od 124 bolesnika u istraživanoj skupini 50,8 % je bilo ženskih (n=63) i 49,2 % muških (n=61). Srednja dob bolesnika bila je 11,5 godina, a medijan 12 godina. Devedeset i četiri od 124 (75,8 %) uzorka negativnih apendektomija pokazivalo je izražene vaskularne kleftove. Širina vaskularnih kleftova je varirala između 140 i 1751 µm. Dvanaest uzoraka (9,7 %) nije pokazivalo znakove vaskularnih kleftova, a 18 uzoraka je imalo djelomične vaskularne kleftove koji nisu penetrirali kroz čitavu debljinu stijenke apendiksa i stoga se nisu mogli izmjeriti. Također smo pokazali statistički značajnu razliku u broju apendiksa koji su sadržavali fekolite u lumenu između istraživane skupine i kontrolne skupine ($p<0,01$). ***Rasprava:*** Negativne apendektomije su i dalje problem u medicinskoj praksi 21. stoljeća. Iako mnogi slučajevi kliničke sumnje na akutni appendicitis mikroskopski ne pokazuju znakove upale, u nekim slučajevima simptomi se mogu povući nakon provedene apendektomije, iako nema patohistoloških znakova upale. U svakodnevnoj praksi primijetili smo da u slučajevima akutnog supurativnog i flegmonoznog apendicitisa gusti upalni infiltrat često prolazi kroz izražene vaskularne kleftove, koje definiramo kao procjepe mišićnog sloja stijenke crijeva (u ovom slučaju apendiksa) kroz koji krvne žile i periferni ogranci živaca prolaze u crijevo. Pokušali smo odrediti značenje ovih vaskularnih kleftova. Sakupili smo 124 uzorka iz arhive našeg Zavoda za patologiju i citologiju, od kojih su svi odstranjeni iz pedijatrijskih bolesnika zbog kliničke sumnje na akutni apendicitis. Nijedan od 124 apendiksa nije ispunjavao naše kriterije za akutni apendicitis. Utvrdili smo da su vaskularni kleftovi bili prisutni u 94 od 124 (75,8 %) uzorka negativnih apendektomija. Također smo izračunali stopu negativne apendektomije za Kliniku za dječje bolesti Zagreb u petogodišnjem razdoblju koja iznosi 9 %. ***Zaključak:*** Naši rezultati pokazuju da su izraženi vaskularni kleftovi u mišićnom sloju stijenke apendiksa često prisutni u uzorcima negativnih apendektomija. Ti kleftovi bi mogli biti uključeni u patofiziologiju akutnog apendicitisa i mogli bi biti među prvim znakovima akutnog apendicitisa.

Ključne riječi: crvuljak, upala crvuljka, vaskularni kleft, stopa negativne apendektomije

THE CONTROLLING NUTRITIONAL STATUS (CONUT) SCORE MIGHT PREDICT SURVIVAL IN MAINTENANCE HEMODIALYSIS PATIENTS

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Malnutrition causes substantial morbidity in maintenance hemodialysis (HD) patients. The Controlling Nutritional Status (CONUT) has emerged as a simple and an easily obtainable tool to comprehensively assess nutrition as it consists of serum albumin levels, absolute lymphocyte counts, and total cholesterol levels. The CONUT has been shown to predict overall survival (OS) in peritoneal dialysis patients. This study investigated whether CONUT might also predict OS in maintenance HD patients. Clinical and laboratory data were retrospectively collected. Survival time was calculated from the first HD until death or last follow-up; survival analyses were performed using the methods of Kaplan-Meier and Cox regression analysis. Eighty-nine patients were included; mean age was 65.76 years (±14), 35 (39.3%) were female, and the mean CONUT was 3. Higher CONUT score correlated with lower low-density liproprotein, higher serum creatinine, higher serum C-reactive protein and higher neutrophil-to-lymphocyte ratio, as well as with a higher incidence of nephrotic proteinuria ($p<0.050$ for all analyses). Univariately, patients with higher CONUT (≥5) had an inferior OS (median 54 vs. 112 months, HR 2.27; $p=0.013$). In the Cox regression analysis, higher CONUT remained independently associated with inferior OS (HR 9.50; $p=0.002$) when adjusted to age, sex, diabetes mellitus and nephrotic proteinuria. Therefore, the CONUT score might identify HD patients at an increased risk of death; however, future studies are needed to elucidate whether CONUT score might be able to guide nutritional support in HD patients.

Key words: malnutrition, inflammation, survival, CONUT, hemodialysis

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INTRODUCTION

Malnutrition and hypoalbuminemia cause substantial morbidity and mortality in hemodialysis (HD) patients (1-4). For this reason, current guidelines recommend nutritional screening for these patients; however, limited evidence exists as to which tool performs best (5).The Controlling Nutritional Status (CONUT) score has emerged as a simple and an easily obtainable tool to comprehensively assess nutrition, as it consists of albumin concentration (indicator of protein reserves), absolute lymphocyte count (indicator of weak immune defense due to malnutrition) and total cholesterol level (indicator of caloric depletion) in peripheral blood (6). This particular index has been shown to be an independent prognostic factor in several cancers (7-10). Moreover, the CONUT score has been recently shown to accurately predict mortality in patients undergoing peritoneal dialysis (11). In this study, we investigated the ability of the CONUT score to predict overall survival (OS) in patients with kidney failure.

PATIENTS AND METHODS

Study design

This was a single-center retrospective study conducted at the Department of Internal Medicine, General Hospital of Šibenik-Knin County, Croatia, in the period between July 2007 and May 2019. Patients undergoing maintenance HD due to kidney failure as defined by the Kidney Disease Improving Global Outcomes (KDIGO) 2012 criteria (12) were retrospectively included. Baseline demographic, clinical and laboratory data were recorded at the time of first HD. Excluded from participation were pregnant women, subjects <18 years of age, and patients with acute kidney injuries requiring HD.

The use of medications was considered significant if prescribed for ≥3 months during the follow-up. Arterial hypertension was defined as the regular use of antihypertensive drugs to control blood pressure or at least two blood pressure measurements of >140/90 mm Hg. Nephrotic proteinuria was defined as >3.5 g/24 h. Erythropoietin was administered to all patients with hemoglobin level <90 g/L despite adequate parenteral iron supplementation (transferrin saturation ≥30%) as *per* KDIGO 2012 guideline 13).

The CONUT score was calculated as described in the original study (6) and in accordance with a tool presented in Table 1. We also evaluated whether this tool might provide additional prognostic information when compared to the Geriatric Nutritional Risk Index (GNRI) and Prognostic Nutritional Index (PNI). The GNRI can be used to assess nutrition in HD patients and was shown to predict OS in these patients (14-16). It can be calculated using body weight, height and serum albumin levels with the formula: GNRI=[1.489×albumin (g/L)]+[41.7×(weight/ideal weight)]. The PNI is a nutritional risk index which also takes into account serum albumin levels and absolute lymphocyte counts, thereby indicating the nutritional and immune status of a patient. It was originally developed to stratify perioperative risk (17) and was shown to predict outcomes in patients with chronic kidney disease (18-20). The PNI can be calculated using the formula: (10 x serum albumin [g/dL]) + (0.005 x lymphocytes/μL).

Statistical analyses

Statistical calculations were performed with MedCalc Statistical Software® (Ostend, Belgium, version 19.7). The Shapiro-Wilk test was used to check for data distribution. Categorical variables were compared using the χ^2-test, whereas the one-way analysis of variance (ANOVA), Mann-Whitney U or Kruskal Wallis test were used to compare continuous variables between patient groups, as appropriate. The Jonckheere-Terpstra trend test was used to test trends for increase in C-reactive protein (CRP) levels and neutrophil-to-lymphocyte ratios (NLR) accross the CONUT scores. Receiver operating curve (ROC) analysis was used for sensitivity and specificity testing. The OS was measured as the time from the first HD until death or the last follow-up visit. Survival analyses were performed using the Kaplan-Meier and Cox regression analysis. Significant p-values were set at <0.050 for all analyses presented.

Ethics

The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional Review Board.

RESULTS

Correlations of the CONUT score with clinical characteristics

Eighty-nine patients were included; mean age was 65.76 years (±14) and 35 (39.3%) were female. The mean CONUT score was 3 (±2) and a total of 25 (28.1%) patients had normal (0-1), 44 (49.4%) had light (2-4) and 20 (22.5%) had moderate (5-8) CONUT score, whereas none of the patients included in this study had severe (9-12) CONUT score.

Patients were then stratified according to the mean CONUT score (0-3 *vs*. 4-8). Clinical characteristics were well balanced, with no differences between the two groups regarding demographics (age and sex), HD-related variables (body weight, body height, body mass index, location of arteriovenous fistula, and presence of central venous catheter), comorbidities (presence of polycystic kidney disease or obstructive uropathy, arterial hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, systemic autoimmune disorders or concomitant cancers), use of medications (statins, uricosurics, aspirin, warfarin, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ARB), steroids and erythropoetins), and the majority of blood cell count components (p<0.050 for all analyses). Expectedly, patients with higher CONUT score had statistically significantly lower serum albumin levels (median 32.7 *vs*. 38 g/L; p<0.001), total cholesterol levels (mean 3.64 *vs*. 4.71 mmol/L; p<0.001) and absolute lymphocyte counts (mean 1280 *vs*. 1500/mm^3; p=0.036), as these three variables are integrated into the CONUT score (Table 1). Similarly, higher CONUT score correlated with lower PNI (median 30.30 *vs*. 37.15; p<0.001). Differences in serum albumin levels might also explain the lower serum calcium levels in patients with higher CONUT score (mean 2.19 *vs*. 2.32 mmol/L; p=0.019). Interesting-

ly, no differences were found in absolute lymphocyte counts between low and moderate CONUT score risk groups (mean 1.273 *vs*. 1.286/mm^3; p>0.050) and only two (2.2%) study patients had absolute lymphocyte count <800/mm^3 (these patients had CONUT scores of 5 and 6). Patients with higher CONUT score also had lower low-density lipoprotein (median 1.86 *vs*. 2.50 mmol/L; p<0.001), but there were no differences with respect to high-density lipoprotein (p=0.135) and serum triglycerides (p=0.068). Even though the proportion of patients receiving erythropoetin despite adequate iron supplementation was similar in both risk groups (82.7% *vs*. 86.4%), patients with higher CONUT score had lower serum hemoglobin levels (mean 94.72 *vs*. 101.76 g/L; p=0.036). Notably, patients with higher CONUT score had lower serum creatinine (median 498 *vs*. 638 μmol/L; p=0.003), most probably reflecting their lower muscle mass. Also, patients with higher CONUT score more often had nephrotic proteinuria (35.1% *vs*. 9.6%, p=0.003), suggesting a glomerular albumin loss (median serum albumin levels was 33 *vs*. 36.9 g/L; p=0.002 for patients with and without nephrotic-range proteinuria, respectively).

Table 1.
The Controlling Nutritional Status (CONUT) score (6).

Variable	Normal	Light	Moderate	Severe
Serum albumin (g/dL)	3.5-4.5	3.0-3.49	2.5-2.9	<2.5
Albumin score	0	2	4	6
Total lymphocyte count (mm^3)	≥1600	1200-1599	800-1199	<800
Total lymphocyte count score	0	1	2	3
Total cholesterol (mg/dL)	>180	140-180	100-139	<100
Total cholesterol score	0	1	2	3
CONUT score	0-1	2-4	5-8	9-12
Assessment	Normal	Light	Moderate	Severe

The CONUT score is calculated as the sum of albumin score, total lymphocyte count score and total cholesterol score.

With respect to inflammatory biomarkers, there were no differences in serum CRP levels (p=0.626) and NLR (p=0.123) between the two groups. However, there was a trend for increase in serum CRP levels (median 1.8 *vs*. 3.45 vs. 3.90 mg/L; p=0.039) and NLR (median 2.45 *vs*. 3.17 *vs*. 3.20; p=0.016) with rising CONUT scores, as shown in Figure 1. Finally, patients with a higher CONUT score also had higher serum immunoglobulin G (mean 13.10 *vs*. 5.87 g/L; p=0.038) and immunoglobulin M levels (mean 0.92 *vs*. 0.33 g/L; p=0.046), whereas there were no differences in serum IgA levels (p=0.288). Statistically significant differences in clinical and laboratory variables between the two groups are summarized in Table 2.

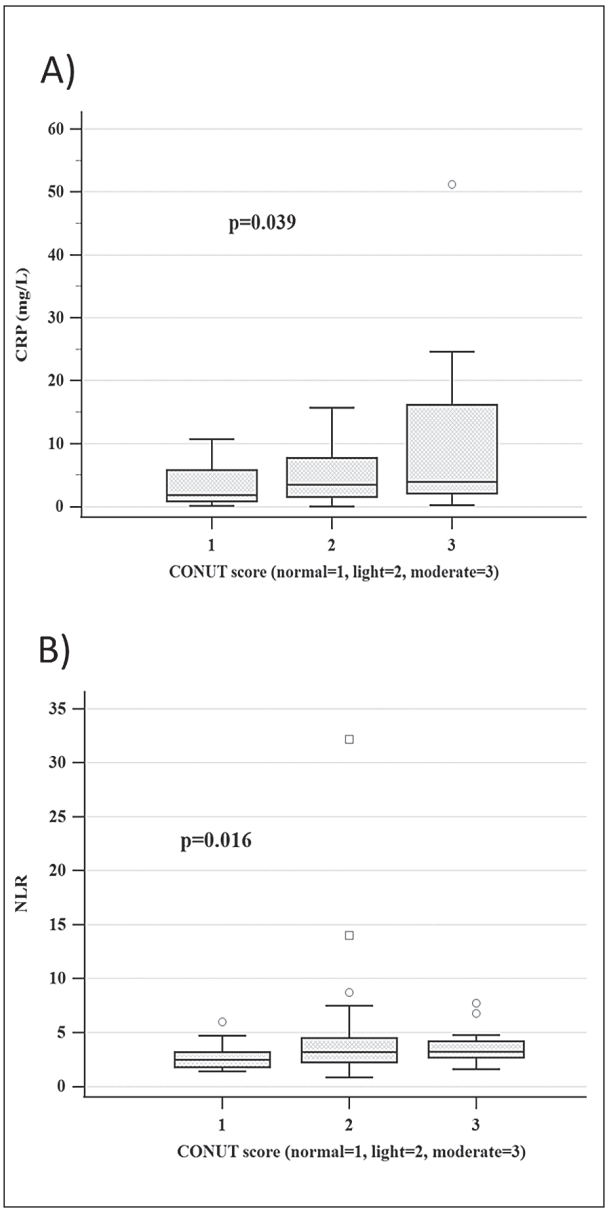

Fig. 1. *An increasing trend in serum C-reactive protein (CRP) levels and neutrophil to lymphocyte ratio (NLR) was found with rising CONUT scores. The Jonckheere-Terpstra trend test was used*

Table 2.
Patient'clinical and laboratory variables that significantly differed according to CONUT score.

Variable	Overall (n=89)	CONUT score 0-3 (n=52, 58.5%)	CONUT score 4-8 (n=37, 41.5%)	p value
Nephrotic proteinuria	18 (20.2%)	5 (9.6%)	13 (35.1%)	**0.003**
Creatinine (µmol/)	584 (IQR 187-1251)	638 (IQR 187-1251)	498 (IQR 227-1091)	**0.003**
Lymphocytes (x10^9/L)	1.41 (SD ±0.50)	1.50 (SD (±0.55)	1.28 (SD ±0.38)	**0.036**
Hemoglobin (g/L)	98.84 (SD ±15.69)	101.76 (SD ±14.91)	94.72 (SD ±16.04)	**0.036**
Serum albumin (g/L)	36 (IQR 24-46.6)	38.1 (IQR 30-46.6)	32.7 (IQR 24-42)	**<0.001**
Total cholesterol (mmol/L)	4.26 (SD ±1.09)	4.71 (SD ±0.93)	3.64 (SD ±1.01)	**<0.001**
LDL (mmol/L)	2.3 (IQR 0.1-4.75)	2.50 (0.1-4.75)	1.86 (IQR 0.3-4.45)	**<0.001**
Serum calcium (mmol/L)	2.27 (SD ±0.26)	2.32 (SD ±0.27)	2.19 (SD ±0.21)	**0.019**
Immunoglobulin G (g/L)	8.97 (SD ±4.93)	5.87 (SD ±3.45)	13.10 (SD ±3.24)	**0.038**
Immunoglobulin M (g/L)	0.59 (SD ±0.41)	0.33 (SD ±0.37)	0.92 (SD ±0.05)	**0.046**

The χ^2, ANOVA one-way analysis of variance, and Mann-Whitney U tests were used. Significant p values are bold and were set at <0.050; CONUT = Controlling Nutritional Status score; LDL = low-density lipoprotein; SD = standard deviation; IQR = interquartile range.

Survival analyses

The median follow-up was 54 (range 6-146) months; 35 (44.3%) patients died during this time. For the purpose of survival analyses, ROC curve with death as a classification variable was created to search for the optimal cut-off value of the CONUT score. The approximate area under the ROC curve (AUC) for the CONUT score ≥5 was 0.667 (±0.061, 95% CI 0.559-0.764; p=0.009). Univariately, patients with a CONUT score of 5-8 had an inferior OS (median OS 54 *vs*. 112 months, HR 2.27; p=0.013), as shown in Figure 2. Additionally, diabetes mellitus (median OS 79 *vs*. 125 months, HR 1.82; p=0.070), age >54 years (median 85 months *vs*. not reached, HR 3.76; p=0.018), lower (<35 g/L) serum albumin levels (HR median 58 *vs*. 112 months, HR 2.04; p=0.031) and lower (≤4.9 mmol/L) total cholesterol levels (HR median 90 months *vs*. not reached, HR 5.0; p=0.010) were associated with inferior OS. In the multivariate Cox regression model, higher CONUT score (5-8) remained statistically significantly associated with inferior OS (HR 9.50; p=0.002), when adjusted to age, sex, diabetes mellitus and nephrotic proteinuria, as shown in Table 3. Of note, using the ROC curve analyses, we could not establish the optimal cut-off values of absolute lymphocyte counts and low-density lipoprotein levels which could have been associated with an inferior OS.

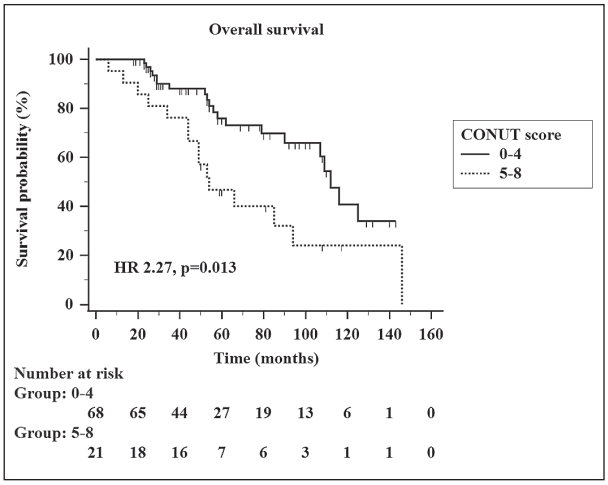

Fig. 2. *Patients presenting with higher Controlling Nutritional Status (CONUT) score had an inferior overall survival. The Kaplan-Meier log-rank test was used*

Table 3.
Prognostic impact of high CONUT score on overall survival remained statistically significant in the multivariate Cox regression model.

Variable	HR	95% CI	p value
CONUT 5-8	9.50	1.54-7.02	**0.002**
Age >54 years	4.53	1.11-13.52	**0.033**
Diabetes mellitus	0.97	0.66-3.48	0.324
Nephrotic proteinuria	0.93	0.24-1.61	0.333
Male sex	2.03	0.24-1.24	0.153

Significant p values are bold and were set at <0.050; CONUT = Controlling Nutritional Status score; HR = hazard ratio, CI = confidence interval.

For final analyses, we set the optimal cut-off levels of the PNI and GNRI at 37.9 and 86, respectively. Univariately, patients having low (<86) GNRI demonstrated inferior OS (median 85 *vs*. 116 months, HR 2.31; p=0.041), whereas patients with low (<37.9) PNI had a trend towards an inferior OS, which barely failed to reach statistical significance (median 79 *vs*. 116 months; HR 1.87; p 0.072). Using the Cox multivariate regression models, we tested performance of the CONUT score when compared to the GNRI and PNI. In the first model, the CONUT score was shown to accurately predict survival (HR 5.63; p=0.017) when adjusted to low (<86) GNRI (HR 1.86; p=0.174), age >54

years (HR 4.72; p=0.029), male sex (4.09; p=0.049), diabetes mellitus and nephrotic proteinuria (p not significant). In the second model, the CONUT score (HR 5.54; p=0.018) and age >54 years (HR 4.98; p=0.025) remained independently associated with inferior OS, whereas low (<37.9) PNI (HR 2.25; p=0.133), sex, diabetes mellitus and nephrotic proteinuria were not (p not significant). Finally, the ROC analysis with death as a classification variable demonstrated no statistically significant differences in the predictive abilities of the GNRI, PNI and CONUT score with respect to OS (p>0.050 for all pairwise comparisons), as shown in Figure 3. However, the AUC for the CONUT score (0.667, 95% CI 0.559-0.764) was higher than that of the GNRI (0.617, 95% CI 0.507-0.718) and PNI (0.593, 95% CI 0.483-0.696).

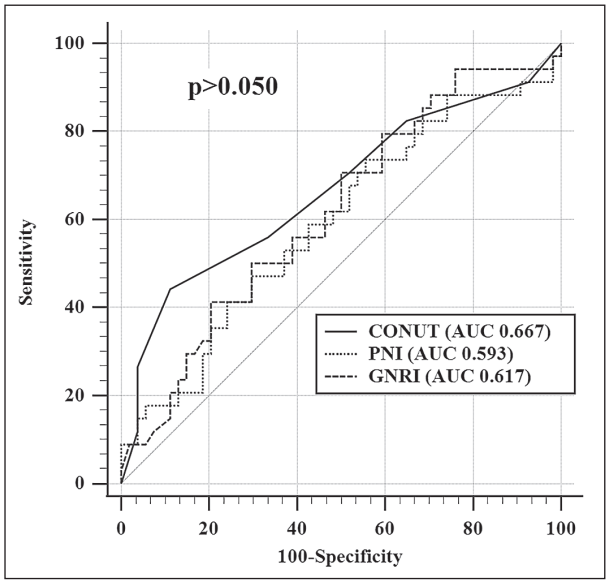

Fig. 3. *There were no statistically significant differences in the predictive abilities of the Geriatric Nutritional Risk Index (GNRI), Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) score with respect to overall survival. The receiver operating curve analysis was used.*

DISCUSSION

To our knowledge, this is the first study to report that higher CONUT score might be prognostic of an inferior OS in kidney failure patients undergoing maintenance HD. Malnutrition has been recognized as a late complication of kidney failure. More importantly, several studies have shown that protein-energy malnutrition in maintenance HD patients is associated with increased morbidity and mortality (1-4); thus, routine nutrition screening is recommended at least bianually in order to identify those at a high nutritional risk (5). For this reason, several risk scores have been developed; however, limited evidence exists to suggest the use of one tool over others. In addition, some indexes can be quite time-consuming as they include a wide set of clinical and laboratory variables (21,22). On the other hand, our study suggests that CONUT score, a comprehensive, yet a simple and an easily obtainable tool, could also be used to rapidly screen maintenance HD patients for nutrition. More importantly, this tool was able to correctly identify HD patients at an increased risk of death. Interestingly, in the multivariate Cox regression models, the CONUT score was associated with an inferior OS when adjusted to the GNRI and PNI rendering them insignificant. This is most probably due to their overlapping prognostic properties as all three risk scores include a related set of variables (i.e. serum albumin levels and lymphocyte counts) and were shown to be similarly prognostic (Figure 3). Nevertheless, the CONUT score includes low total cholesterol levels, a risk factor associated with inferior OS in our study. In addition, the AUC of the CONUT score was higher than that of the GNRI and PNI; thus, it seems that the CONUT score might provide additional information and perhaps identify an additional proportion of HD patients at an increased risk of death. However, future studies on a larger number of patients are needed to confirm our observations. Also, as this study only assessed baseline nutritional status, longitudinal assessment of nutrition is lacking and prospective studies are needed to elucidate whether the CONUT score might be able to guide nutritional support in order to improve outcomes in maintenance HD patients.

Besides nutrition, higher CONUT score might also reflect a higher degree of systemic inflammation, as it is derived from serum albumin concentration and absolute lymphocyte counts. Studies have shown that proinflammatory cytokines (such as interleukin-6 or tumor necrosis factor-alpha) can cause decreased serum albumin concentrations through the increased consumption and *via* down-regulation of albumin synthesis in hepatocytes (23,24). Furthermore, elevated NLR has been shown to correlate with higher inflammation, lower hemoglobin and serum creatinine levels, and to accurately predict mortality among HD patients (25,26). Interestingly, higher CONUT score was associated with lower hemoglobin, higher CRP, elevated NLR and higher serum immunoglobulin levels in our study as well; therefore, higher CONUT score could also reflect on another adverse pathophysiological process in HD patients, systemic inflammation (1-4).

Interestingly, higher CONUT score in our HD patients seemed to be mostly caused by lower protein reserves and caloric depletion (as indicated by markedly lower serum albumin and total cholesterol levels in the higher CONUT score risk groups). More im-

portantly, both lower serum albumin and total cholesterol levels were associated with inferior OS. This paradoxical association of hypocholesterolemia and OS in maintenance HD patients was recognized a decade ago and was most pronounced in hypoalbuminemic patients and in those with a low dietary protein intake, indicating a detrimental effect of malnutrition on survival (27). On the other hand, absolute lymphocyte counts were similar between the light and moderate risk groups (in both groups, the mean lymphocyte count was >1200/mm^3, assigning only 0 or 1 points to the majority of patients). Of note, only two patients in our study had absolute lymphocyte count <800/mm^3; none of them had a severe CONUT score. This might represent a selection bias with exclusion of the severely malnourished patients who could have experienced unfavorable outcomes prior to study entry. In addition, during the study period, patients might have been exposed to different enteral supplements (i.e. patients with cancers, systemic autoimmune disorders or nephrotic-range proteinuria) that could have modulated different patient characteristics (such as serum albumin and total cholesterol levels), as well as patient outcomes. For this reason, future studies are needed to analyze clinical correlations and outcomes of severely malnourished patients (according to the CONUT score), as well as the ability of the CONUT score to identify HD patients at an increased risk of infection due to secondary lymphocyte depletion.

Other notable limitations of this study were its single-center retrospective design and small number of patients included. Due to the retrospective design of the study, we were also unable to assess other important anthropometric measures at baseline, i.e. body composition or waist circumference (5).

CONCLUSION

The results of this study suggest that the CONUT score might be used for rapid nutritional screening and for prediction of mortality in maintenance HD patients; however, our observations need confirmation on larger datasets, or even better, in a prospective trial.

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SAŽETAK

NUTRITIVNI ZBROJ *(CONTROLLING NUTRITIONAL STATUS – CONUT)* MOŽE PREDVIDJETI PREŽIVLJENJE BOLESNIKA NA HEMODIJALIZI

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Pothranjenost uzrokuje značajan pobol i smrtnost bolesnika na hemodijalizi (HD). *Controlling Nutritional Status* (CONUT) je jednostavan nutritivni zbroj koji cjelovito procjenjuje uhranjenost, a sastoji se od serumske koncentracije albumina, apsolutnog broja limfocita i koncentracije serumskog kolesterola. Ova unicentrična retrospektivna studija analizirala je prediktivnu sposobnost zbroja CONUT da procijeni preživljenje bolesnika na HD. Ukupno preživljenje mjereno je kao vrijeme od prve HD do smrti ili posljednjeg pregleda bolesnika, a krivulje preživljenja uspoređene su Kaplan-Meirovom metodom, dok je Coxova regresijska metoda primijenjena u multivarijatnim analizama. Uključeno je 89 bolesnika, od toga 35 (39,3 %) žena; srednja dob bila je 65,76 godina (±14). Srednji zbroj CONUT bio je 3. Viši zbroj CONUT korelirao je s nižim koncentracijama serumskog lipoproteina niske gustoće, višim serumskim kreatininom, višim serumskim C-reaktivnim proteinom i višim omjerom neutrofila/limfocita, kao i s većom učestalošću nefrotske proteinurije (p<0,050 za sve analize). U univarijatnoj analizi je viši zbroj CONUT (≥5) bio povezan s lošijim preživljenjem (medijan 54 prema 112 mjeseci, HR 2,27; p=0,013). U multivarijatnoj Coxovoj regresijskoj analizi je viši CONUT ostao nezavisno povezan s lošijim preživljenjem (HR 9,50; p=0,002) kada je bio ispravljen za dob, spol, šećernu bolest i nefrotsku proteinuriju. Zaključno, zbroj CONUT može identificirati bolesnike na HD s povišenim rizikom od smrti. Potrebne su dodatna istraživanja kako bi se analizirala sposobnost zbroja CONUT da usmjeri nutritivnu potporu u bolesnika na HD.

Ključne riječi: pothranjenost, upala, preživljenje, CONUT, hemodijaliza

Acta Med Croatica, 75 (2021) 131-135 *Pregled*

ENCEFALOPATIJA UZROKOVANA PRIMJENOM METRONIDAZOLA

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Metronidazol je antibiotik koji se koristi u liječenju anaerobnih bakterijskih i parazitarnih infekcija. Kao rijetka nuspojava primjene ovog lijeka može se javiti encefalopatija. Najčešće primijećeni klinički simptomi uključuju dizartriju, nestabilnost u hodu i/ili ataksiju. Encefalopatiju uzrokovanu primjenom metronidazola potrebno je diferencijalno dijagnostički razlikovati od drugih mogućih uzroka encefalopatije. Uz kliničku sliku i podatak o primjeni metronidazola od pomoći su magnetska rezonancija mozga (MRI) - T2 i prikaz FLAIR te neurološka dijagnostika koja uključuje elektroencefalografiju (EEG), laboratorijsku obradu i lumbalnu punkciju. Tipični nalazi MRI mozga u T2 i FLAIR tehnici pokazuju hiperintenzitet koji u većini slučajeva zahvaća *nucleus dentatus* malog mozga, dijelove moždanog debla te *splenium corpus callosuma.* Ponekad je potrebno učiniti i gensko testiranje kako bi se isključili i vrlo rijetki uzroci encefalopatije. Neurološke promjene uzrokovane primjenom metronidazola najčešće su reverzibilne i povlače se nakon ukidanja metronidazola iz terapije. U liječenju ove vrste encefalopatije može se primijeniti metilprednizolon.

Ključne riječi: metronidazol, nuspojave, encefalopatija

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UVOD I CILJEVI RADA

Metronidazol je antibiotik u medicinskoj upotrebi od 1959. godine, a primjenjuje se u profilaksi i liječenju anaerobnih bakterijskih i parazitarnih infekcija. Pokazao je značajnu učinkovitost u terapiji anaerobnih mikroorganizama poput *Clostridium difficile*, sojeva *Bacteroides, Fusobacteria*, *Gardnerelle vaginalis*, *Trichomonas vaginalis*, anaerobnih koka te amebijaze i *Gardiae lambliae*. Metronidazol ima široku primjenu te se koristi u liječenju kožnih bolesti poput rozaceje, dentalnih infekcija, infekcija kostiju i zglobova, ginekoloških infekcija, endokarditisa, sepse, peritonitisa, infekcija respiratornog trakta i svih oblika amebijaze. Koristi se i u liječenju Crohnove bolesti te kao profilaksa prije kirurških zahvata (1,2). Lijek se dobro podnosi i nuspojave su rijetke. Prema uputama Sažetka o svojstvu lijeka navode se vrlo rijetke nuspojave kao što su grčevi, psihičke smetnje poput osjećaja smetenosti ili halucinacija, poteškoće s vidom kao što su zamućenje vidnog polja ili dvoslike, kožni osip, crvenilo i vrućina lica, glavobolja, tamnija boja mokraće, pospanost, omaglica, bolovi u mišićima i zglobovima. Navedene nuspojave su vrlo rijetke s učestalošću od 1 na 10 000 bolesnika. Uz to se u literaturi navode iznimno rijetke pojave mučnine, abdominalne boli i proljeva (1,3-7). Praćenje primjene pojedinih antibiotika pokazuje povremenu pojavu neurotoksičnosti. Ova je nuspojava rijetka pri primjeni antibiotika, ali ima široku lepezu mogućih kliničkih manifestacija. Zamijećene su mialgije, mučnina, povraćanje, smetnje vida i cerebelarni simptomi (5,7). Predmet našeg interesa je pojava neurotoksičnosti u bolesnika liječenih metronidazolom.

PRIKAZ LITERATURE

Uvidom u dostupnu literaturu, tijekom primjene metronidazola opisani su slučajevi optičke neuropatije, periferne neuropatije i encefalopatije. Encefalopatija je iznimno rijetka nuspojava liječenja metronidazolom i opisuju se samo pojedinačni slučajevi (1). Pregledom dostupne literature u ovom je članku evidentirano 15 pojedinačnih prikaza slučajeva pojave metronidazolom inducirane encefalopatije. Kao najčešći klinički simptomi zabilježeni su nestabilnosti pri hodu i/ili ataksija, zatim dizartrija te znakovi encefalopatije i fokalni neurološki ispadi. Od ostalih simptoma još su zabilježeni mučnina, povraćanje, vrtoglavica, anksioznost, epileptički napadaji, glavobolja, zamagljen vid i mialgija. Prema prikazanim slučajevima, raspon dobi bolesnika bio je od 11 do 86 godina, od toga 9 žena i 6 muškaraca. Također se u prikazu literature osvrnulo i na japansku studiju (opisano niže u tekstu) koja je uključivala prikaz 32 bolesnika koji su razvili encefalopatiju pri primjeni metronidazola (11). 65-godišnja žena produženo je liječena zbog kolitisa uzrokovanog *Clostridium difficile* te je razvila mentalno oštećenje, smetnje govora i nestabilnost (2). Opisan je slučaj 11-godišnjeg dječaka koji je primao oralnu terapiju lijeka zbog liječenja upotrebom *Fusobacterium meningitidis*, uz pojavu mučnine, povraćanja, nestabilnosti i vrtoglavice (3). Učestale nuspojave su mučnina, povraćanje i hipersenzitivnost. Uz to je 38-godišnji muškarac koji je liječen zbog apscesa mozga imao i glavobolju i fokalni neurološki ispad (4). 72-godišnja žena koja je tretirana metronidazolom subakutno je razvila dizartriju, nestabilnost pri hodu i encefalopatiju uz izraženu anksioznost. Dijagnoza encefalopatije potvrđena je tipičnim nalazom MRI mozga koji je pokazao simetrične hiperintenzitete u T2 prikazu (6). 36-godišnja žena je tijekom dugotrajnije primjene metronidazola tijekom 40 dana razvila mialgiju, mučninu, povraćanje, zamagljenje vida, cerebelarne simptome kao što su smjerni nistagmus, ataksija i nesposobnost u tandem hodu (7). U opisanim slučajevima konačna dijagnoza postavljena je temeljem MRI mozga. Neuroradiološki su prikazane bilateralne hiperintenzivne lezije u spleniju korpusa kalozuma, mezencefalonu i nukleusu dentatusu u T2/FLAIR MRI prikazu (7,8). Poseban oprez pri primjeni metronidazola potreban je kod bolesnika koji već imaju cirozu jetre ili nakon transplantacije jetre. Mogući porast razine amonijaka povećava mogućnost nastanka encefalopatije. U slučaju crijevnih tegoba s kroničnim proljevom povećana je sklonost nastanku encefalopatije uzrokovane dodatnom primjenom metronidazola (9,10). U jednoj japanskoj studiji praćena su 32 bolesnika koji su primali metronidazol intravenski zbog apscesa mozga (35,3 % bolesnika), apscesa jetre (17,6 % bolesnika) i infekcije *Clostridium difficile* (14,7 % bolesnika). Većina bolesnika imala je disfunkciju jetre, šećernu bolest i druge metaboličke poremećaje te maligne ili hematološke bolesti. Nakon produžene terapije metronidazolom, u prosjeku 61,3 dana, pojavile su se dizartrija, ataksija i znakovi encefalopatije. Encefalopatija je potvrđena nalazom MRI mozga. MRI mozga pokazao je visoki intenzitet signala bilateralno u nukleusu dentatusu (11). Prikazan je i slučaj 84-godišnje žene koja je u razdoblju od dva mjeseca u dva navrata liječena oralnom terapijom metronidazolom (500 mg 3 puta na dan) zbog infekcije *Clostridium difficile* udružene s proljevom. Tijekom hospitalizacije javila se dizartrija, ataksija, nestabilnost pri hodu sa znakovima subakutnih cerebelarnih sindroma što su sve klinički znakovi encefalopatije. MRI mozga u FLAIR prikazu pokazao je obostrani hiperintenzitet u nukleusu dentatusu malog mozga, kolikuli superior i periakveduktalnoj sivoj tvari. Isključen je deficit vitamina B_1, B_9 ili B_{12}. Simptomi dizartrije i nestabilnost pri hodu postupno su se povukli isključivanjem metronidazola iz terapije (12).

Opisan je slučaj 65-godišnje žene s hepatitisom B i cirozom jetre koja je tri tjedna bila na terapiji metronidazolom zbog kolecistitisa. Razvila je kliničku sliku encefalopatije. MRI mozga pokazao je simetrično obostrano hiperintenzitet u T2 prikazu i restrikciju difuzije obostrano u nukleusu dentatusu, korpusu kalozumu, moždanom deblu, *pedunculus colliculi superioris*, *capsulae internae* i bijeloj tvari mozga. Laboratorijski nije utvrđen elektrolitski disbalans, a nisu zabilježeni ni epileptički napadaji. Lumbalna punkcija nije učinjena zbog koagulopatije i trombocitopenije. Empirijski je ordinirana visoka doza tiamina (13). Utvrđeno je da se metronidazol često primjenjuje u bolesnika s bolestima jetre i Crohnovom bolesti. Tijekom produženog uzimanja lijeka razvija se nestabilnost pri hodu, dizartrija, epileptički napadaji i encefalopatija. Dugoročno uzimanje ovog lijeka povećava vjerojatnost nastanka metronidazolom izazvane encefalopatije (14). Kod 83-godišnje žene koja je bila hospitalizirana zbog ponovljenog kolitisa izazvanog infekcijom *Clostridium difficile* kolitisa klinička dijagnoza encefalopatije potvrđena je MRI nalazom; u T2 prikazu nađene su promjene u dorzalnom dijelu ponsa i nukleusu dentatusu. Prekidom primjene metronidazola postupno su iščeznuli i simptomi encefalopatije, a MRI-om utvrđene lezije postupno su regredirale (15). Kronični alkoholičar, 32-godišnji muškarac s multiplim apscesima jetre koji je uzimao metronidazol šest tjedana, imao je brojne epileptičke napadaje, poremećaj osjeta i trnce u stopalima. MRI-om mozga utvrđene su reverzibilne promjene koje su zahvatile nukleus dentatus i splenij korpusa kalozuma tipične za encefalopatiju (16). Prikazan je i bolesnik s alkoholnim oštećenjem jetre koji je uz to imao i rekurentni piogeni kolangitis zbog čega je bio duže vrijeme na terapiji metronidazolom. Zbog cerebelarne ataksije, dizartrije i mentalne konfuzije učinjen je i MRI, nalaz kojeg je tipičan za encefalo-

patiju uzrokovanu metronidazolom. Sve navedeno potvrdilo je dijagnozu metronidazolom uzrokovane encefalopatije. Zbog prekomjerne doze lijeka nastala je kumulacija doze od 22 grama što je zbog dekompenzirane ciroze jetre i posljedičnog porasta u cerebrospinalnom likvoru uzrokovalo encefalopatiju (17). Bolest jetre kao što je ciroza, udružena s primjenom nekih antibiotika, uključujući i primjenu metronidazola, povećava rizik od nastanka encefalopatije (18,19). Boyer i sur. ispitivali su mutaciju ETHE1 gena koja je odgovorna za etilmalonsku encefalopatiju i terapiju metronidazolom (20). Nadalje, ispitivana je uloga deficita tiamina u nastanku metronidazolske encefalopatije (21). Metronidazolom uzrokovana encefalopatija utvrđena je u liječenju 43-godišnjeg muškarca zbog apscesa jetre u trajanju od 45 dana. U kliničkoj slici dominirali su cerebelarna ataksija, diskoordinacije udova, nerazgovjetan govor, dezorijentiranost, agitacija. Smetnje su prestale dva dana nakon ukidanja terapije metronidazolom. Krvne pretrage i analiza cerebrospinalnog likvora bili su uredni. MRI mozga u T2 i FLAIR tehnici pokazao je obostrani simetrični hiperintenzitet koji zahvaća i nukleus dentatus malog mozga, dorzalni dio ponsa i *colliculi inferior*es moždanog debla. DWI prikazom utvrđena je restrikcija difuzije u spleniju korpusa kalozuma. Nakon 15 dana od prestanka uzimanja lijeka promjene na mozgu postupno su nestale (22). 64-godišnji muškarac s Crohnovom bolesti liječen je povremeno metronidazolom peroralno i ponekad intravenskom primjenom tijekom 13 godina. U jednom navratu tijekom intravenske primjene metronidazola kao komplikacija su se pojavile smetnje govora prema tipu afazije i slabost muskulature. MRI mozga pokazao je hiperintenzitet obostrano u medijalnom dijelu talamusa, moždanog debla i tegmentumu ponsa. Isključenjem metronidazola iz terapije postupno su umanjene i kliničke tegobe i MRI promjene na mozgu. Dva mjeseca nakon encefalopatije zaostale su tek blage kognitivne smetnje (23). 86-godišnja žena liječena je zbog piogenog spondilitisa lumbalne kralježnice. Dijagnostičkom obradom i uzorcima biopsije utvrđena je gram-pozitivna anaerobna bakterijska infekcija usne šupljine. U terapiju je uključen metronidazol u peroralnom obliku u dozi od 1500 mg/dan. Četrdeset i četiri dana nakon primjene lijeka javila se utrnulost jezika, dizartrija i smetnje gutanja. Dijagnoza je postavljena temeljem kliničke slike i MRI mozga koji je u T2 prikazu pokazao promjene koje postupno regrediraju tijekom 14 dana od prekida uzimanja metronidazola (24). Diferencijalno dijagnostički je temeljem laboratorijskih i MRI nalaza potrebno razlikovati etilmalonsku encefalopatiju koja je posljedica rijetke autosomno recesivne mitohondrijske bolesti (25). Metronidazolom inducirana encefalopatija može uzrokovati i cerebelarnu disfunkciju uz oštećenje mentalnog statusa te ekstrapiramidne simptome. To je zabilježeno u 86-godišnje žene koja je uzimala metronidazol u liječenju infekcije *Clostridium difficile*. Uz to imala je motornu slabost lijevih udova. Kompjutorizirana tomografija (CT) pokazala je intracerebralnu hemoragiju, ali CT angiografija nije pokazala promjene krvnih žila. MRI mozga je u FLAIR tehnici pokazao hiperintenzitet u nukleusu dentatusu, splenij korpusa kalozuma i stražnjem dijelu moždanog debla (26). U slučaju 72-godišnje žene s uznapredovalom Crohnovom bolesti koja je liječena metronidazolom zabilježeno je postupno progresivno usporenje misaonog tijeka uz smetnje hoda, sve do kome. MRI mozga pokazao je hiperintenzitet u T2 prikazu u korpusu kalozumu, nukleusu ruberu i nukleusu dentatusu. Terapija metronidazolom je prekinuta, ali je bolesnica razvila sepsu koja je rezultirala smrtnim ishodom. Obdukcijom su utvrđene promjene nukleusa rubera uz mikroskopski dokazanu nekrozu i demijelinizaciju (27).

RASPRAVA

Metronidazol je sintetski antibiotik koji se najčešće koristi u liječenju anaerobnih infekcija i protozoa. Neurotoksičnost antibiotika manifestira se u tri klinička fenotipa: kao encefalopatija udružena s epileptičkim napadajima ili mioklonizmima nakon nekoliko dana uzimanja cefalosporina i penicilina, kao encefalopatija karakterizirana psihozom nakon nekoliko dana primjene lijeka (u slučaju primjene kinolona, makrolida i prokain penicilina) i encefalopatija udružena sa cerebelarnim znakovima uz MRI jasne znakove nakon nekoliko dana primjene metronidazola (5).

Encefalopatija je neuobičajena i vrlo rijetka nuspojava kod bolesnika koji uzimaju metronidazol primijenjen intravenski ili u peroralnom obliku (13). U tom slučaju govorimo o metronidazolom induciranoj encefalopatiji.

Potrebno je razlikovati rijetke slučajeve etilmalonske encefalopatije koja je posljedica rijetke autosomno recesivne mitohondrijske bolesti uzrokovane bialelnom abnormalnom varijantom ETHE1 gena koji kodira mitohodrijsku sumpor-dioksigenazu. Bolest karakterizira neurorazvojni poremećaj i propadanje te pojava piramidnih i ekstrapiramidnih znakova uz pojavu petehija, kroničnog proljeva i ortostatske akrocijanoze. Laboratorijskom obradom utvrđen je porast laktata u serumu, C4, C5 acilkarnitina i pojačano izlučivanje etilmalonične kiseline urinom te značajno isobutirglicina i 2-metilbutirglicina (25,28).

Encefalopatija u bolesnika s kroničnim bolestima koji uzimaju metronidazol zahtijeva širu laboratorijsku i posebno neuroradiološku obradu koja obuhvaća MRI mozga u T2 i FLAIR prikazu koje pokazuju karakteri-

stične promjene u korpusu kalozumu, nukleusu dentatusu i nukleusu ruberu, a moguće i drugim strukturama mozga. MRI je od pomoći i za diferencijalnu dijagnostiku prema drugim oblicima encefalopatija (29). Svakako je potrebno diferencijalno dijagnostički razlikovati Wernickeovu encefalopatiju kao i rijetke etilmalonične encefalopatije. Stoga je potrebno uz MRI mozga učiniti i širu diferencijalno dijagnostičku laboratorijsku obradu koja uključuje i gensko testiranje (25,28,30). Istraživanja pokazuju da bolesnici s encefalopatijom uzrokovanom metronidazolom. uz kliničku sliku kojom dominiraju smetnje govora i cerebelarni znakovi, konfuzna stanja i oštećenje kognitivnih funkcija, imaju i specifične prikaze MRI mozga s hiperintenzitetima u T2 i FLAIR prikazu obostrano u nukleusu dentatusu malog mozga, moždanom deblu i nukleusu ruberu. Uz to se registriraju promjene encefalograma (EEG) uz theta aktivnost simetrično u frontalnoj regiji koja se širi anterio-posteriorno u skladu s kliničkim pogoršanjem (31-33). Svakako je potrebno diferencijalno dijagnostički razlikovati encefalopatiju uzrokovanu metronidazolom od drugih mogućih uzroka encefalopatija, kako različitih sistemskih bolesti, tako i genetski uvjetovanih poremećaja. Na temelju kumulativne doze ili trajanja primjene metronidazola, nije moguće predvidjeti kada će pacijenti razviti neurološke simptome (34). Neurološke promjene su najčešće reverzibilne i prestankom uzimanja metronidazola, uz primjenu pulsne terapije metilprednizolonom, smetnje regrediraju tijekom nekoliko dana do nekoliko tjedana (31).

ZAKLJUČAK

Metronidazol je antibiotik koji se već desetljećima koristi širom svijeta u liječenju bakterijskih i parazitarnih infekcija. Neurotoksičnost je rijetka nuspojava primjene ovog lijeka, a encefalopatija se kao posljedica primjene metronidazola pojavljuje iznimno rijetko. Encefalopatija se dijagnosticira temeljem kliničke slike, neuroradiološke obrade, laboratorijskih testova te ako je potrebno i temeljem genskih testiranja.

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SUMMARY

ENCEPHALOPATHY CAUSED BY THE APPLICATION OF METRONIDAZOLE

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Metronidazole is an antibiotic used for treating anaerobic bacterial and parasitic infections. A rare side effect of using this drug is encephalopathy. The most commonly observed symptoms include dysarthria, gait instability, and/or ataxia. Metronidazole induced encephalopathy should be differentiated from other possible causes of encephalopathy. Clinical picture with data on metronidazole application, as well as magnetic resonance imaging (MRI) of the brain, T2 and FLAIR sequences, neurological diagnostic procedures such as electroencephalography (EEG), laboratory tests and lumbar puncture should be performed. Typical brain MRI findings in T2 and FLAIR technique show hyperintensity, which in most cases affects dentate nucleus of the cerebellum, parts of brainstem, and splenium *corporis callosi.* Genetic testing is sometimes required to distinguish some rare causes of encephalopathy. Neurological changes due to metronidazole application are most often reversible and vanish after metronidazole withdrawal. Use of methylprednisolone in treating this type of encephalopathy is sometimes helpful.

Key words: metronidazole, side effects, encephalopathy

COVID-19 PANDEMIC AND KIDNEY TRANSPLANTATION

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Infections are a common complication arising after kidney transplantation with a high rate of morbidity and mortality. Since the beginning of the COVID-19 pandemic, it has been reported that the kidney transplant recipient population have the worst outcome and highest rate of mortality. The pandemic greatly influences the management of chronic kidney failure and transplantation programs. This review describes clinical presentation and risk factors linked to COVID-19, the management and outcomes, COVID-19 vaccination in kidney transplant recipients, and the impact of COVID-19 on renal transplantation programs.

Key words: COVID-19, kidney transplantation, vaccination, outcome, SARS-CoV-2

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was found to cause COVID-19 and has spread in waves throughout the world since the end of 2019. Until May 28, 2021, more than 168 million COVID-19 confirmed cases, 3.5 million deaths, and more than 1.5 billion doses of vaccine administered worldwide have been recorded (1).

Kidney transplant recipients (KTR) are considered to be at a high risk of COVID-19, with the worst outcome due to immunosuppression and clinical presentation that might differ from what is seen in the general population. This review mainly focuses on clinical presentation and risk factors of COVID-19 in KTR, immunosuppression management and outcomes, and the influence of the COVID-19 pandemic on renal transplant programs.

CLINICAL PRESENTATION AND RISK FACTORS

As in the general population, KTR with COVID-19 infection mainly present with fever and respiratory symptoms such as cough and dyspnea. In some kidney transplant patients, fever may be absent (2). More recently, multiple studies have elucidated that COVID-19 is a systemic disease often manifesting with gastrointestinal (GI) symptoms, liver injury, cardiac involvement, encephalitis, atypical stroke, and acute kidney injury (AKI), in addition to endothelial cell injury and coagulopathy, the likely mediators of multiorgan involvement (3). Symptoms such as cough, shortness of breath, myalgia, headache, sore throat, and GI symptoms are more common in KTR than the typical COVID-19 presentation. Additionally, several unreported symptoms such as chest tightness and pain, coryza, dehydration, conjunctivitis, dizziness, and weight loss appeared in the SARS-CoV-2 positive KTR. Non-white ethnicity, obesity, diabetes, and asthma/chronic pulmonary diseases are risk factors independently associated with COVID-19 disease in patients with kidney transplants and immunosuppression modulation (4). Other risk factors are advanced age, male gender, not to mention immunosuppression itself. The burden of comorbidities such as diabetes and hypertension, which are mostly reported as significant factors influencing the outcome of COVID-19, as well as smoking and cardiovascular disease further compromise outcomes in KTR with COVID-19 (2,3,5).

END-STAGE RENAL DISEASE AND COVID-19

End-stage renal disease (ESRD) is considered when chronic injury to the kidney leads to decreased functioning of the organ with a glomerular filtration rate (GFR) below 15 mL/min/1.73 m^2 (6). At this level, renal replacement therapy (RRT) with either peritoneal dialysis, hemodialysis, or kidney transplantation should be initiated. In a review study, Valeri reports an infection rate of COVID-19 between 11%-26% among patients with ESRD, with a mortality rate of up to 24%-27%, which is 6-7 times higher than the rate of 4% reported in the global population (7). Thus, given the immunocompromised nature of ESRD and the high comorbidity burden seen in patients with kidney failure, patients with ESRD are among the most vulnerable populations to COVID-19.

Similar to the general population, the most common presenting symptoms in ESRD patients remain fever and cough (8,9). In contrast, Ferrey *et al*. described an atypical presentation with symptoms of gastroenteritis in ESRD patients, which was similar to KTR (10). Adapa *et al*. report on acute kidney injury (AKI) to be an independent risk factor for mortality in COVID-19 patients, with an incidence of 3%-15%. In patients with severe infection requiring intensive care, the rates of AKI increased significantly from 15% to 50% (11). Another concern is the high incidence of AKI in patients infected with COVID-19 requiring hospital resources that strain intensive care units and ventilator capacity and renal replacement resources (7). In COVID-19 patients with severe AKI and with established ESRD, continuation of their RRT is vital for survival. It is recommended that healthcare personnel should follow what the Centre for Disease Control recommends for personal protective equipment and safety guidelines during their interactions with those patients to decrease the spread of infection and nosocomial acquisition in RRT centers (11).

It has been recommended that hospitalized patients with COVID-19 who experience any form of AKI should be followed up closely after discharge to assess the ongoing kidney function (12).

OUTCOMES OF COVID-19 IN KIDNEY TRANSPLANT RECIPIENTS

The mortality rate of COVID-19 in KTR is at least four times higher than in the general population (2). Elias *et al*. report a high mortality rate among KTR with COVID-19, fluctuating between 20% and 28% as compared with 1%-5% mortality in the general population (4). Coronavirus pandemic is too recent and currently, data on the clinical course, imaging features, and outcomes in KTR have not yet been fully elucidated. In a study on 12 patients, where ten were admitted to the intensive care unit, nine were intubated, eight died of severe COVID-19 pneumonia and acute respiratory distress syndrome (ARDS), and four were discharged after complete recovery, Abrishami *et al*. report that the most common pattern of lung involvement was bilateral involvement with a diffuse pattern and posterior segmental distribution. Ground glass opacity, a feature highly suggestive of COVID-19, was observed in all cases and consolidation in the majority of them (Figure 1).

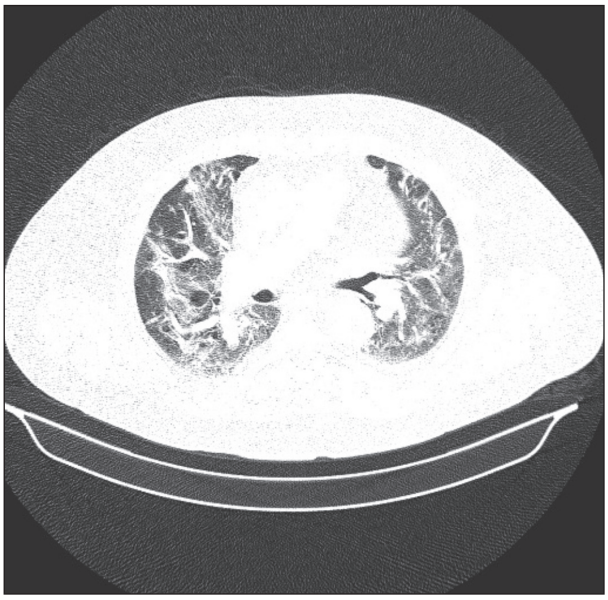

Fig. 1. *Chest computerized tomography in a renal transplant recipient with SARS-CoV-2 infection. Bilateral ground glass opacities with a diffuse pattern are present with areas of consolidation.*

The authors concluded that interlobular septal thickening, multilobar patterns, consolidative lesions, and a high score for lung involvement were more frequent among patients with poor outcomes and complicated cases with acute respiratory distress syndrome (ARDS) (13). Jawdeh reports an elevated incidence of AKI and a mortality rate of 13%-30%, which is higher than that in the general population (~5%). This could be attributed to the increased prevalence of comorbidities in addition to the immunosuppressed state leading to severe COVID-19 (3). Other studies have also found male gender to be associated with high mortality in COVID-19 infected KTR (3,14). Craig-Schapiro *et al*. also report that there was the need for RRT in hospitalized patients and that high inflammatory markers such as D-dimer, procalcitonin, and C-reactive protein were associated with high mortality (14). The management is mainly performed in patients presenting with severe symptoms such as dyspnea and

requiring mechanical ventilation, with immunosuppression reduction and supportive therapy in most patients (4,15).

MANAGEMENT OF COVID-19 IN KIDNEY TRANSPLANT RECIPIENTS

Immunocompromised patients, including those on immunosuppression following solid organ transplantation, are considered to be at a high risk of severe COVID-19. At this time, supportive care is paramount to combat this virus in solid organ transplant recipients. Little data are currently available regarding optimal medical management of KTR testing positive for SARS-CoV-2, including strategies for reducing or modifying immunosuppression. Elias *et al*. report that managing immunosuppression in patients with COVID-19 disease is arduous (4). Corticosteroids are a cornerstone of many immunosuppressive regimens; however, their use in SARS-CoV-2 remains controversial (4,16). Increased mortality recorded in transplant recipients with COVID-19 corroborates the role of diminished T- and B-cell immunity as a predisposing factor for severe infection. It would be reasonable to hold the antimetabolite in those with moderate disease and continue low-dose calcineurin inhibitor with or without glucocorticoids. In patients with severe disease and in critically ill patients, it may be justifiable to hold all maintenance immunosuppression except for steroids (3,17). Banerjee *et al*. suggest that antiproliferative agents (mycophenolate mofetil and azathioprine) be stopped at the time of admission to the hospital, the dose of prednisolone be either unchanged or increased, and tacrolimus dose be reduced. In severe infections (requiring intubation and ventilation), an argument can be made for stopping calcineurin inhibitors completely while maintaining corticosteroid therapy (5). This is in line with our approach that resulted in 7% mortality rate. An individual approach is mandatory with the decision based on disease severity, patient characteristics, and immunologic risk.

In a national survey in the United States, Boyarsky *et al*. report that antimetabolites were reported to have been stopped by 92.3% of respondents and calcineurin inhibitors were reduced by 26.9% of respondents (18). It has been reported that 81% of COVID-19 patients present with mild disease and can be managed at home. In contrast, severe and critical COVID-19 disease should be managed with prompt hospitalization while ensuring appropriate infection control and supportive care, with empiric treatment for bacterial infections, prevention of venous thromboembolism, and avoiding nebulized medications (2). Since patients should consider the risks and benefits of any treatment before giving their consent, the risks associated with minimizing or discontinuing immunosuppressants, thus potentially changing the fate of functioning kidney transplantation, should be clearly explained so that patients can make a well-informed decision (19).

INFLUENCE OF COVID-19 PANDEMIC ON RENAL TRANSPLANT PROGRAMS

The COVID-19 pandemic has pushed the world to rethink, reshape and adapt in the way everything works. Regarding renal transplant programs, the fear of allegedly increased susceptibility to infections in KTR due to immunosuppression has forced many centers to shut down their transplantation unit or change the paradigm and thus the routine of workflow. The reduction in transplantation volume during this time is partly due to concerns about the potential increased susceptibility and worsened outcomes of COVID-19 in immunosuppressed recipients (14). Loupy *et al*. report on strong association between rising coronavirus infections and marked reduction in the overall number of solid-organ transplantation, even in geographic regions with a low infection prevalence (20). In a national survey conducted in the United States linked to COVID-19 and transplantation, Boyarsky *et al*. report on complete suspension of living donor transplantations by 71.8%. However, most deceased donor programs in the United States continued to function with some restrictions (18), whereas in the United Kingdom, kidney transplant programs had to suspend temporarily both the deceased and living donor transplantation (21). The underlying reasons were to release/create more intensive care beds, liberate the workforce to support the intensive care unit, and, more importantly, prevent increase in mortality due to COVID-19 in immunosuppressed individuals (20). Concerning transplant procedures, SARS-CoV-2 infection could be missed in both donors and recipients who are asymptomatic, owing to the sensitivity issues in the RT-PCR test.

Additionally, in the immediate postoperative period and after hospital discharge, transplanted patients have increased susceptibility to SARS-CoV-2 infection due to induction therapy and immunosuppressive treatment (22). Until today, insufficient evidence is available to consider kidney transplantation as a safe procedure in COVID-19 pandemic areas. In emergencies, e.g., in cases of no vascular access, unfeasible dialysis, or a hyperimmune state, the benefits might outweigh the risks of kidney transplant (22). Kidney organs are not readily available and the number of patients on the waiting list keeps growing. All around the world guidelines are being set to increase the safety peri-, during, and post-transplantation procedures during the current pandemic, and specifically to avoid nosocomial COVID-19 infections.

The number of kidney transplantations in Croatia has dramatically decreased over the last year. Faced with the pandemic spreading in waves, the country has answered the epidemiologic challenges. However, the number of transplantations performed has fallen to the levels achieved during the war.

COVID-19 VACCINATION IN KIDNEY TRANSPLANT RECIPIENTS

The vaccine-preventable disease can cause adverse patient and allograft outcomes in KTR and live-attenuated vaccinations are contraindicated in KTRs due to the risk of infection (23). With the current COVID-19 pandemic, Ikizler *et al*. provide data suggesting that complete vaccination protocols should be implemented in patients receiving maintenance hemodialysis and in KTR (24). In the absence of confirmed association between natural SARS-CoV-2 infection and acute allograft rejection in KTR (25,26), it is unlikely that vaccine antigens would precipitate clinically significant immune responses to renal allografts. Thus, recommendations are to administer SARS-CoV-2 vaccine pre-transplantation when possible or at least at 3 months post-transplantation. Nevertheless, future evaluations of SARS-CoV-2 vaccine platforms in KTR must confirm their safety and immunogenicity (25). Considering only humoral response, Cucchiari *et al*. report that S-specific antibodies were developed only by 29.9% of patients in their study population (27). Grupper *et al*. report on a 37.5% antibody response rate after the second dose of the BNT162b2 (Pfizer) vaccine (26). Boyarsky *et al*. have recently reported a higher seroconversion of 54% in patients receiving an mRNA-vaccine, either mRNA-1273 (Moderna) or BNT162b2 (Pfizer) (28). Considering the percentage of patients who had positive S-ELISpot after the second dose, the percentage of patients who developed either humoral or cellular response increased to 65% and half of the antibody-negative patients had developed positive ELISpot. This finding highlights that patients may be protected against SARS-CoV-2 despite the absence of S antibodies (27).

We were the first to report COVID-19 in patients who had completed the vaccination program (29-31), indicating a high risk of nonresponding to the vaccination.

CONCLUSION

Kidney transplant recipients remain a population at risk of COVID-19 infection due to their immunosuppression status, high morbidity and mortality. All over the world, the pandemic of COVID-19 has forced transplant programs to either shut down or to readapt. Vulnerable KTR patients who are not yet vaccinated or are non-responsive to mRNA vaccines should be closely followed up and sanitary protection measures strictly respected.

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SAŽETAK

PANDEMIJA COVID-19 I TRANSPLANTACIJA BUBREGA

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Infekcije su česta komplikacija nakon transplantacije bubrega. Povezane su s visokom stopom pobola i smrtnosti. Od samog početka pandemije COVID-19 uočeno je da bolesnici s transplantiranim bubregom imaju lošije ishode i višu stopu smrtnosti u usporedbi s općom populacijom. Pandemija COVID-19 je značajno utjecala na zbrinjavanje bolesnika sa završnim stadijem kronične bubrežne bolesti i na transplantacijske programe. Prikazujemo klinički nastup, čimbenike rizika, liječenje i ishode COVID-19 u populaciji bolesnika s transplantiranim bubregom, kao i utjecaj pandemije na transplantacijske programe.

Ključne riječi: COVID-19, transplantacija bubrega, cijepljenje, ishodi, SARS-CoV-2

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UTJECAJ ANTIEPILEPTIČNE TERAPIJE NA RAZINU TJELESNE AKTIVNOSTI KOD BOLESNIKA S EPILEPSIJOM

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Cilj ovog istraživanja bio je ispitati utjecaj antiepileptične terapije na razinu tjelesne aktivnosti kod osoba s epilepsijom. Uzorak ispitanika činilo je 140 osoba oboljelih od epilepsije, 73 muškarac i 67 žena prosječne dobi od 24 do 45 godina (35,15 ± 10,01), a istraživanje je provedeno na Klinici za neurologiju KBC-a Sestre milosrdnice u Zagrebu. Testiranje se provodilo upitnikom *International Physical Activity Questionnaire* (IPAQ), koji je sadržavao 5 varijabli: posao, prijevoz, kućanski poslovi i briga za obitelj, sport i sportska rekreacija, vrijeme provedeno sjedeći. Korištene su i varijable o trajanju bolesti, učestalosti napada, vrsti epileptičnog napada te vrsti liječenja koje su dio općih podataka iz dokumentacije ispitanika. Dobiveni rezultati pokazuju kako je najčešća niska razina tjelesne aktivnosti (TA) kod osoba sa statusom nezaposlen, koji boluju više od 15 godina i imaju više od 15 napada tijekom godine. Kod osoba s generaliziranim napadima također je zabilježena niska razina TA, a visoka kod osoba sa žarišnim napadima. Muškarci za razliku od žena češće bilježe visoku razinu TA kao i zaposlene osobe. Bolesnici liječeni monoterapijom češće prakticiraju višu razinu TA za razliku od onih koji u svom liječenju koriste dva i/ili više antiepileptika (politerapija), gdje je zabilježena niska razina TA.

Ključne riječi: epilepsija, antiepileptici, tjelesna aktivnost, kvaliteta života

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UVOD

Epilepsija se definira kao skup neuroloških smetnji koje se javljaju zbog abnormalnih, ponavljajućih poremećaja u funkciji živčanog sustava čija je klinička prezentacija epileptični napad. Epileptični napad ili ataka označava povremeno, neregulirano, ekscesivno pražnjenje (izbijanje) živčanih stanica u različitim dijelovima mozga. Ovisno o tome u kojem dijelu mozga se poremećaji pojavljuju, napadaji se različito manifestiraju: gubitak ili promjena stanja svijesti, abnormalna motorička aktivnost (najčešće konvulzije), psihički i osjetni poremećaji, promijenjeno ponašanje i/ili poremećaji autonomnog živčanog sustava. Epilepsija je uz glavobolju jedna od najčešćih primarnih bolesti živčanog sustava. Prema Europskoj deklaraciji o epilepsiji donesenoj 2011. godine u Europskoj uniji od epilepsije boluje 6 000 000 ljudi, a svake je godine 300 000 novo dijagnosticiranih osoba, dok ih je u Hrvatskoj oko 40 000 (1-3).

Uzroci nastanka epilepsije su različiti. Prema zadnjoj klasifikaciji epilepsije kao etiološki čimbenici nabrajaju se genetski, strukturni, metabolički, imunološki, infekcije, a u nekim slučajevima etiologiju nije moguće jasno definirati. Dijagnoza epilepsije utvrđuje se sukladno svjetskim i hrvatskim smjernicama. Liječenje epilepsije može se svrstati u dvije skupine: farmakološko liječenje, odnosno primjena antiepileptika i kirurško liječenje u indiciranim slučajevima. Primjena antiepileptika može izazvati nuspojave koje su specifične za određene lijekove, kao i utjecati na ostale lijekove koje bolesnici uzimaju u terapiji (4,5).

Bavljenje sportom i tjelesnom aktivnošću (TA) osoba s epilepsijom u prošlosti je bilo znatno ograničeno,

pa su te osobe bile u lošijem zdravstvenom stanju u odnosu na opću populaciju. Tijekom povijesti oboljeli od epilepsije bili su stigmatizirani, izolirani od zajednica pa čak i zatvarani. Tijekom 70-ih godina prošlog stoljeća dolazi do potpunog obrata i umjesto ograničavanja kretanja, osobe s epilepsijom potiču se da se uključe u sportsku aktivnost. Iako brojna istraživanja pokazuju dobrobit redovite TA kod bolesnika s epilepsijom, često se postavlja pitanje može li tjelesna aktivnost dovesti do povećanja broja ili pojave epileptičkih napada i u kojoj mjeri TA utječe na svakodnevno funkcioniranje (6-8).

CILJ ISTRAŽIVANJA:

Cilj ovog istraživanja bio je ispitati utjecaj antiepileptika na razinu tjelesne aktivnosti kod osoba s epilepsijom.

ISPITANICI I METODE

Za potrebe ovog istraživanja koristio se uzorak od 140 osoba oboljelih od epilepsije, 73 muškarca i 67 žena prosječne dobi od 24 do 45 godina (35,15 ± 10,01), a istraživanje je provedeno u Kliničkom bolničkom centru Sestre milosrdnice na Klinici za neurologiju u Zagrebu. Podatci su prikupljeni uz informirani pristanak ispitanika te uz odobrenje Etičkog povjerenstva KBC-a Sestre milosrdnice. Svi podatci bili su prikupljeni u skladu s etičkim i bioetičkim principima, na način da su privatnost i zaštita tajnosti podataka u potpunosti osigurani sukladno nacionalnoj i međunarodnoj regulativi.

Uzorak varijabli čini hrvatska verzija Internacionalnog upitnika o tjelesnoj aktivnosti (*International Physical Activity Questionnaire* - IPAQ). Ovaj upitnik služi za mjerenje tjelesne aktivnosti vezane uz zdravlje te se podatci uspoređuju na međunarodnoj razini. Procjenjuje se tjelesna aktivnost populacije od 15 do 69 godina i preporuke su da se ne ispituju osobe mlađe ili starije od navedene dobne granice. Upitnik ima dužu i kraću verziju, te se ispitivanje može provesti telefonskim putem ili samostalnim ispunjavanjem. U ovom istraživanju korištena je duža verzija koja se sastoji od 5 kategorija, a to su: posao, prijevoz, kućanski poslovi i briga za obitelj, sport i sportska rekreacija te vrijeme provedeno sjedeći. Varijable se procjenjuju na način da se vrednuje intenzitet, koji je podijeljen na hodanje, vožnju biciklom te umjerenu i visoku tjelesnu aktivnost, a ukupni rezultat dobio se zbrajanjem trajanja (minute) te učestalosti (u danima) navedenog intenziteta. Za svaku vrstu tjelesne aktivnosti postoji određena energetska potrošnja koja se mjeri metaboličkim ekvivalentom tjelesne aktivnosti (MET), pa se hodanje izražava s 3,3. MET-a, vožnja biciklom sa 6,0 MET-a, dok je umjerena tjelesna aktivnost izražena sa 4,0 MET-a, a visoka s 8,0 MET-a (1 MET = 3,5 mL $O_{2/}$ min/kg). Vrijednost svake pojedine varijable računala se tako da se množila vrijednost MET-a s trajanjem aktivnosti u minutama/satima i broja dana u tjednu, a konačni rezultat IPAQ upitnika dobiva se zbrajanjem rezultata svake varijable (9).

Korištene su i varijable o trajanju bolesti, učestalosti napada, vrsti epileptičnog napada te vrsti liječenja, obiteljskom i poslovnom statusu, edukaciji, koje su dio općih podataka iz dokumentacije ispitanika.

Tablica 1.
Demografski podatci ispitanika

Demografski podatak	**Vrijednost**
Dob (godine-aritmetička sredina ±SD)	35,15± 10,01
Spol (ukupan broj muškarci/žene)	73/67
Zaposleni (%)	64,13
Nezaposleni (%)	35,8
Edukacija ≤12 godina (%)	23,12
Edukacija ≥12 godina (%)	76,88
U braku (%)	46,15
Nisu u braku (%)	53,85
Imaju djecu (%)	26,17
Nemaju djecu (%)	73,83
Trajanje bolesti (godine aritmetička sredina ±SD)	9,12 ± 6,03
Učestalost napada (po godini aritmetička sredina ±SD)	8,28 ± 7,56
Generalizirani napadi	32,52
Žarišni napadi	56,41
Monoterapija	56,12
Politerapija	43,88

Statistika

Podatci su obrađeni u programu *Statistica (TIBCO Software, Inc*. Kalifornija, SAD), a demografski su podatci analizirani korištenjem varijance ANOVA. Za analizu rezultata IPAQ testiranja korišten je hi-kvadrat test; statistička značajnost određena je na razini od $p<0,05$.

REZULTATI

Rezultati dobiveni u ovom istraživanju pokazuju da je 2/3 ispitanika radno sposobno, odnosno da su zaposleni bez obzira na to što im je dijagnoza epilepsija. Također je zanimljiv podatak i to da je 76,88 % ispitanika uspješno završilo neki oblik edukacije u trajanju duže od 12 godina uz redovitu kontrolu napada primjenom antiepileptika. Podatak o tome da 53,78 % ispitanika nije u braku ukazuje kako osobe oboljele od epilepsije teže ostvaruju bračnu zajednicu i potomstvo. Trajanje bolesti je u prosjeku 9 godina, a učestalost napada procjenjuje se oko 8 tijekom godine. Najzastupljenija vrsta napada su žarišni, dok su generalizirani napadi manje zastupljeni. Što se tiče farmakološkog liječenja ispitanici većinom koriste jedan antiepileptik (monoterapija), a 43,88 % ih koriste politerapiju kao sredstvo kontrole napada.

U tablici 2. vidljivi su odnosi između promatranih varijabli koje su vrednovane u IPAQ upitniku i tjelesne aktivnosti niske, umjerene i visoke razine. Muškarci i žene podjednako se slabo bave tjelesnom aktivnošću što nam ukazuje i *p* vrijednost tih varijabli. Statistički značajna razlika pronalazi se kod osoba sa statusom zaposlenih koji češće prakticiraju visoku razinu tjelesne aktivnosti, dok je razina TA niska kod nezaposlenih ljudi. Osobe s edukacijom manjom od 12 godina također češće prakticiraju TA više razine nego osobe čija edukacija prelazi 12 godina. Njihova TA većinom je niže razine. Kada je riječ o ispitanicima koji su u bračnoj zajednici, vidljivo je da je tjelesna aktivnost manje primjenjivana nego kod onih koji nisu u bračnoj zajednici i bave se visokom razinom TA. Rezultati pokazuju nisku razinu tjelesne aktivnosti kod osoba s djecom u odnosu na osobe bez potomstva koje se više bave TA umjerenog intenziteta. TA niskog intenziteta zastupljena je kod ispitanika čije je trajanje bolesti više od 15 godina, kao i onih koji imaju više od 15 napada godišnje. Različita razina TA vidljiva je kod različitih vrsta napada, stoga je visoka razina zastupljena kod osoba sa žarišnim napadajem, a niska kod generaliziranih. Također, primjena terapije djeluje na razinu TA. Rezultati pokazuju kako se osobe liječene jednim lijekom (monoterapija) bave visokom razinom TA češće nego oni koji koriste politerapiju.

Tablica 2.
Odnos varijabli promatranih u upitniku IPAQ

Demografski podatak	Niska razina tjelesne aktivnosti (%)	Umjerena razina tjelesne aktivnosti (%)	Visoka razina tjelesne aktivnosti (%)	p vrijednost*
Dob	32	31	30	0,57
Spol				
Žene	34%	34	32	0,62
Muškarci	32	33	35	0,59
Zaposlenje				
Zaposleni	22	36	42	0,01
Nezaposleni	44	38	18	0,02
Edukacija				
Edukacija ≤12 godina	26	33	45	0,01
Edukacija ≥12 godina	46	27	27	0,02
Bračni status				
U braku	33	31	30	0,12
Nisu u braku	29	35	36	0,15
Potomstvo				
Imaju djecu	38	29	33	0,09
Nemaju djecu (%)	29	36	35	0,34
Trajanje bolesti				
≤ 15 godina	33	31	34	0,81
≥ 15 godina	66	17	16	0,.01
Učestalost napada				
≤ 15 napada	34	40	26	0,03
≥ 15 napada	85	10	5	0,01
Vrsta napada				
Generalizirani napadi	66	24	10	0,01
Žarišni napadi	19	37	44	0,04
Vrsta terapije				
Monoterapija	21	23	56	0,02
Politerapija	33	31	36	0,07

p<0,5. p-vrijednosti smatraju se statistički značajnima

RASPRAVA

Život osoba s epilepsijom tijekom prošlosti nije bio nimalo lagan. U većini kultura takve su osobe bile smatrane opsjednutima te su često bile izolirane iz zajednice, katkad i zatvarane te im je bila ograničena mogućnost bavljenja TA što je rezultiralo i slabijim

zdravstvenim statusom bolesnika (10). Kako je vrijeme odmicalo, brojna istraživanja upućuju na to da se osobe uključuju u različite oblike TA. U studijama se navode mnogobrojni pozitivni učinci TA kod osoba s epilepsijom, kao što su smanjenje učestalosti napada, unaprjeđenje aerobnog kapaciteta i kardiovaskularnog sustava te općenito kvalitete života. Anksioznost i depresija najčešći su psihički poremećaji s kojima se bolesnici susreću te TA ima pozitivan učinak i u području mentalnog zdravlja. Naime, razina endorfina, hormona sreće, povećava se za vrijeme TA te je na taj način povezana s redukcijom stanja anksioznosti, dok na depresiju ima utjecaj razina serotonina koja se također povećava tijekom TA

Naše istraživanje je pokazalo kako se ispitanici bave višom razinom TA kada koriste samo jedan lijek (monoterapija) za kontrolu napada zbog manje mogućnosti pojavljivanja nuspojava što određeni antiepileptik izaziva, ali i zbog dobre kontrole napada. Oni bolesnici kod kojih je teže postići kontrolu napada, koriste politerapiju kao način liječenja. Takvi ispitanici se globalno manje bave TA zbog mogućnosti pojavljivanja većeg broja nuspojava kako je riječ o kombinaciji dvaju ili više lijeka. Kvaliteta života također je ocijenjena kao bolja kod ispitanika koji su koristili monoterapiju u odnosu na politerapiju (9-13).

TA nižeg intenziteta, poput hodanja uočava se kod osoba s generaliziranim napadima. Dobiveni rezultati kod žarišnih napada su potpuno različiti te se ispitanici bave visokom razinom TA. Kada je riječ o zaposlenju, osobe s epilepsijom zbog bolesti su stigmatizirane te ih poslodavci rjeđe zapošljavaju. Ako je uspostavljena adekvatna kontrola napada, takve osobe dobro obavljaju svoj posao, dok status zaposlenosti uvelike utječe na razinu TA. Zbog lošije kontrole napada, nuspojava lijeka kao i psihičkih problema što uzrokuje sama epilepsija, niska razina TA zastupljena je kod nezaposlenih ljudi u odnosu na zaposlene čija je razina TA visoka. Stigma bolesti koja prati osobe s epilepsijom dosta utječe na njihovo samopouzdanje, društveni život i bračni status. Brak je manje zastupljen u osoba s epilepsijom nego kod zdravih ljudi što pokazuju i naši rezultati, a razlog tomu je veliki utjecaj epilepsije na emocionalni i psihički status oboljelih osoba. Iako je bračno zajedništvo bitan faktor u poboljšanju kvalitete života bolesnika, u žena je veća vjerojatnost da neće stupiti u bračnu zajednicu i ako stupe, veća je stopa razvoda nego kod muškaraca s istom dijagnozom. Vidljiva je razlika u razini TA u različitom bračnom statusu gdje se vjenčane osobe globalno manje bave TA nego osobe koje nisu u braku, a čija je razina TA visoka (14).

Na razinu TA utječu i razni čimbenici epilepsije poput trajanja bolesti kao i učestalost napada. Utjecaj TA na aerobni kapacitet osoba s epilepsijom potvrđen je u programu intenzivnog vježbanja tijekom 4 tjedna u eksperimentu gdje je zabilježen porast aerobnog kapaciteta. Program je utjecao i na smanjenje učestalosti napada, a razina antiepileptika u krvi nije se promijenila. Aerobnim načinom vježbanja, odnosno niskim intenzitetom, utječe se na smanjenje učestalosti napada i to je razlog zašto je razina TA niskog intenziteta češće zastupljena kod osoba koje imaju više od 15 napada godišnje (15).

Veća mogućnost ozljeđivanja povezana je s učestalosti napada te je i to jedan od razloga niskog intenziteta TA. Trajanje bolesti uvelike određuje TA pa je tako zabilježena niska razina, ako bolest traje duže od 15 godina, neovisno o učestalosti napada. Na razinu TA utječu brojni faktori, od različitih vrsta napada, vrste liječenja pa sve do čimbenika iz svakodnevnog života. Uz primjerenu kontrolu napada antiepilepticima i uz njihove nuspojave, razina TA može se povećavati prateći napredak bolesnika te sam utjecaj antiepileptika na njegovo cjelokupno stanje (16).

ZAKLJUČAK

Pozitivan utjecaj TA odnosi se na smanjenje učestalosti i broja napada, utjecaj na motivaciju, razvoj socijalnog i društvenog života te kognitivnog i psihološkog aspekta osobe. Razina TA u ovom istraživanju uvelike je određena vrstom napada, godinama bolesti, količini napada godišnje, vrstom liječenja te socijalnim okolnostima ispitanika. Osobe s generaliziranim napadima prakticiraju nisku razinu TA kao i nezaposlene osobe, osobe koje boluju duže od 15 godina te imaju više od 15 napada godišnje. Također oni koji se liječe s dva ili više antiepileptika prakticiraju nisku razinu TA zbog više nuspojava koje se mogu pojaviti te slabije kontrole napada. Oni koji su duže godina bili educirani kao i oni koji su zaposleni, te bolesnici koji su na monoterapiji prakticiraju višu razinu TA. Visoka razina TA kod bolesnika sa žarišnim napadima postoji jer su napadi manje ograničavajući od generaliziranih te je razina samopouzdanja veća. U liječenju bolesnika s epilepsijom od velike je važnosti svakom bolesniku primijeniti individualizirani pristup. Treba odabrati optimalan antiepileptik koji će biti primjeren spolu, dobi i komorbiditetima bolesnika te koji će uz minimalni broj nuspojava omogućiti optimalnu kvalitetu života, pa i razinu tjelesne aktivnosti. Optimalna razina tjelesne aktivnosti će dodatno doprinijeti boljem osjećanju bolesnika, višoj razini samopouzdanja te boljoj kvaliteti svakodnevnog funkcioniranja.

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SUMMARY

EFFECTS OF ANTIEPILEPTIC DRUGS ON THE LEVEL OF PHYSICAL ACTIVITY IN PATIENTS WITH EPILEPSY

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The objective of this study was to examine the effects of antiepileptic drugs on the level of physical activity in people with epilepsy. We included 140 patients suffering from epilepsy, 73 men and 67 women, average age 24-45 years (35.15± 10.01). The study was conducted at Sestre milosrdnice University Hospital Centre, Department of Neurology in Zagreb. The patients were evaluated by the International Physical Activity Questionnaire (IPAQ) that comprises of 5 domains: work, transport, household chores, and care for the family, sporting activities and recreation, as well as sedentary time. The variable of disease duration was also used, as well as the variables of the seizure incidence, type of epileptic seizures, and type of treatment, which are included in general information provided in medical documentation. According to the findings, unemployed persons suffering from epilepsy for over 15 years with over 15 seizures throughout the year most frequently showed low levels of physical activity. Low levels of physical activity were also identified in persons with generalized seizures, whereas persons with focal seizures showed high levels of physical activity. Men and employed persons more frequently showed high levels of physical activity as opposed to women. Patients on monotherapy more frequently showed higher levels of physical activity as compared with those using more than two antiepileptic drugs, i.e. those on polytherapy, who showed low levels of physical activity.

Key words: epilepsy, antiepileptic drugs, physical activity, quality of life

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GUILLAIN-BARRÉ SYNDROME AND ATYPICAL VARIANTS IN CHILDREN: A CROATIAN SINGLE TERTIARY CENTER EXPERIENCE

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Aim: To depict heterogeneous clinical features of atypical Guillain-Barré syndrome (GBS) variants overlapping between different GBS types and subtypes. *Methods:* Retrospective analysis of data comprising neurological features, cerebrospinal fluid (CSF) analysis, ganglioside antibody testing results, electromyography (EMG) findings, brain and spinal magnetic resonance imaging (MRI) in all pediatric patients with GBS treated during a 10-year period at a tertiary center. *Results:* Twenty-three children were treated for GBS during the study period. Atypical variants were found in five patients and included bifacial and severe pharyngocervicobrachial weakness of descending type, sixth nerve lesion accompanied with lower extremity paresthesias, sensory atactic neuropathy and facial nerve lesion, acute ptosis with mydriasis and incomplete Miller Fisher syndrome, and bilateral facial nerve paresis (one case each). Initial CSF analysis revealed mostly normal protein level in atypical variants. MRI evaluation was normal in all atypical variants except for enhancement of the cervical nerve roots in a patient with pharyngocervicobrachial subtype. EMG performed in the first two weeks showed prolonged distal latency and proximal conduction block in 3/5 patients, in elicitable nerves and axonal loss on upper extremities in a patient with pharyngocervicobrachial subtype, and absent F-waves and neural potentials in 3/5 patients. Slight decrease of motor conduction velocity was present in 2/5 patients in distal nerve segments. Antiganglioside antibodies were positive in 4/5 patients. *Conclusion:* Clinical manifestations of GBS are very variable, whereas atypical variants/overlaps are not so uncommon. This study supports the proposed hypothesis of continuous spectrum of GBS requiring reconsideration of the existing diagnostic criteria for classic GBS in pediatric population supported by recently proposed (published) diagnostic guidelines.

Key words: Guillain-Barré syndrome, polyneuropathy, atypical, children

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INTRODUCTION

Guillain-Barré syndrome (GBS) is the most common acute peripheral neuropathy in children. Still, its pathogenesis is not yet completely understood, with a broad spectrum of signs and symptoms, nadir within four weeks from onset, and recovery in a few weeks (1,2). The incidence of GBS in children varies between 0.4 and 1.3/100,000 *per* year, being more common in children aged 10-18 years (1-5). GBS is an immune-mediated postinfectious heterogeneous disorder which encompasses different typical (classic) and atypical, localized and incomplete forms indicating a spectrum of disease (6-9). Classic GBS includes acute axonal motor neuropathy (AMAN), acute axonal motor and sensory neuropathy (AMSAN) if additionally sensory fibers are affected, and acute inflammatory demyelinating polyneuropathy (AIDP). Classic variants are characterized by certain clinical features such as history of antecedent infection (respiratory or gastrointestinal), monophasic disease course and rapidly progressive symmetric, bilateral limb weakness with areflexia or hyporeflexia accompanied with a typical finding of cerebrospinal fluid (CSF) albumin cytologic dissociation (raised protein concentration, normal cell count, although normal protein content does not

exclude GBS), positive antiganglioside antibodies, and neurophysiological evidence for axonal and/or demyelinating neuropathy. All mentioned above support the diagnosis of GBS, but are not specific, therefore should not be relied upon, especially at the inception of symptoms (7,10-12). Electrophysiologic abnormalities are often delayed, thus repeated neurophysiologic testing is sometimes needed. As the first electrophysiologic abnormalities occur, i.e. prolongation of F wave and distal latency, repeated testing is not mandatory (4,13). Therefore, diagnosis of GBS is initially dependent on unspecific clinical manifestations including pain, numbness, paresthesias, and ataxia (14). Involvement of respiratory muscles (respiratory failure in up to 20%) or cranial nerves (in 30%-50% of cases) may develop, as well as hyperreflexia or normal reflexes in 10% of cases (4,7,14). Unusual presentations and atypical variants lead to misdiagnosis and delayed management, thus GBS remains a challenge for practitioners (15). Differential diagnosis is rather broad. Certain mimics of acute flaccid paraparesis complicate diagnosis, especially of atypical/incomplete GBS variants due to similarity to the overlapping syndrome (7,8,16). Therefore, neuroimaging plays an important role in diagnostic pathway by excluding other causes of acute neuromuscular paralysis (7). Even though the outcome is generally favorable with self-limitating course of the disease, autonomic system could be affected (cardiac arrythmias, respiratory insufficiency) leading to lethal outcome in 5%-13% of pediatric cases (17). Atypical variants are more likely to have rapid deterioration with increasing severity of disability scores (mean and at nadir), cranial nerve involvement, dysautonomia (Erasmus GBS Respiratory insufficiency score, urinary incontinence) with relative preservation of muscle strength in the extremities (6,7,18-21). Furthermore, chronic demyelinating polyneuropathy (CIDP) may develop in 3%-5% of GBS patients. Therefore, early diagnosis and management is important for timely monitoring of complications and rational therapeutic approach including plasma exchange (PE), intravenous immunoglobulins (IVIG), and supportive measures (physiotherapy, analgesia due to neuropathic pain) (4,7,10,12,21). We conducted this study with the purpose to present clinical pattern and outcome in pediatric patients with GBS and atypical forms, treated in a Croatian tertiary center.

PATIENTS AND METHODS

This was a retrospective case-series single center study. Medical records of all patients with GBS treated from 2005 to 2014 in a pediatric tertiary center (Department of Pediatrics, Zagreb University Hospital Centre) were evaluated. Patients included in the study met diagnostic criteria for GBS (7). Patients with positive medical history of previous neurological signs and symptoms and abnormal psychomotor development were excluded from the study. Pediatric neurologist reviewed medical files of the patients. The following data were extracted from medical files: age, gender, neurological features, CSF findings, ganglioside antibody studies, electromyography (EMG), brain and spinal magnetic resonance imaging (MRI). Serum samples were analyzed for possible causative bacterial (*Campylobacter jejuni*, *Borrelia burgdorferi* and *Mycoplasma pneumoniae*) or viral etiology (Epstein-Barr virus (EBV), cytomegalovirus (CMV)). The GBS classic subtypes or variants according to electroneurographic studies were documented as AMAN and AIDP. EMG was performed by expert pediatric neurologist with concentric needles; motor fibers were studied by needle recording and surface electrode stimulation, while sensory fibers were studied by orthodromic recording from wrist and ankle. Compound muscle action potential amplitude (CMAP), motor nerve conduction velocity (MNCV), neural potential amplitude, sensory nerve conduction velocity (SNCV), F-wave latency, distal latency (DL) and proximal to distal CMAP (P/D) ratio were measured. Recruitment pattern and spontaneous activity were recorded by needle electrode in small hand muscles and extensor brevis muscles. Motor conduction studies were polysegmentally determined and were performed on peroneal, ulnar and median nerves. In each patient, three to four nerves were examined. Normal values and electrophysiologic criteria for demyelination and axonal degeneration were referred to accepted and proposed ones (14). Children's surface body temperature was between 36.9 °C and 37.0 °C axillary. Serum IgG and IgM anti-ganglioside antibodies (anti-GM1, anti-GD1a, anti-GD1b, anti-GQ1b) were measured by enzyme-linked immunosorbent assay (ELISA) (Gan-gliocombi, Bühlmann Laboratories AG, Basel, Switzerland). GBS disability scale was used to assess the severity of disease (18).

RESULTS

Overall, 23 patients with GBS were treated during the ten-year period (Table 1), 18 of them with typical GBS (12 male; age 2 to 15 years). Atypical variants were found in 5 patients (4 male; age 2 to 10 years) and included bifacial and severe pharyngocervicobrachial weakness of descending type, sixth nerve lesion accompanied with lower extremity paresthesias, sensory atactic neuropathy accompanied by facial nerve lesion, acute ptosis with mydriasis and incomplete Miller Fisher syndrome, and bilateral paresis of facial nerve (one case each). Detailed patient characteristics and evaluation is shown in Table 1. Representative cases of atypical variants are presented below.

Case 1
A 9-year-old boy presented with weakness of upper extremities and swallowing. Bilateral facial nerve and unilateral abducent nerve lesion, plegia of upper limbs, hyperreflexia, neck weakness and hyperhidrosis were observed. On day 8 of disease, the patient developed lower limb paresis and weak cough reflex. GBS disability score was categorized as bedridden or chair bound (modified Rankin score 4). His condition deteriorated during the third week of disease. Lower limbs recovered first after four weeks.

Case 2
A 6-year-old boy presented with right eye pain and diplopia. Unilateral lesion of abducent nerve, left leg weakness, bilateral hyperreflexia and paresthesias with positive plantar extensor response on the left foot were observed.

Case 3
A 10-year-old boy presented with progressive generalized ataxia, dizziness and unstable gait. Limb paresthesias and mild bilateral facial nerve lesion, distal limb hypesthesia and decreased pain sensitivity were observed. He was unstable on Romberg test as well. GBS disability score was 4.

Case 4
A 5-year-old boy was admitted due to sudden onset of ophthalmoparesis accompanied by mydriasis and low intensity headache. Anisocoria, ptosis and nystagmus on the right eye were noticed. GBS disability score was 2.

Case 5
A 2-year-old girl presented with bilateral intermittent ptosis on both eyes, asymmetric grimacing, and decreased tendon reflexes on both upper and lower extremities. GBS disability score was 1.

Table 1. *Demographics, clinical profile, evaluation and treatment of studied patients*

Patients treated for GBS (N=23)	Typical („classic") GBS (N=18)	Atypical GBS/GBS variants ("chameleons") (N=5)				
		PCB /GBS – LS	MFS - IF	SAN/MFS - IF	MFS - IF	GBS - LS
Age (years)	Median 6.5 (range 2 -15)	9	6	10	5	2
Gender	12 male, 6 female	Male	Male	Male	Male	Female
Antecedent infection	Respiratory 6/18- 2 *M. pneumoniae*, 1 VZV IgM positive in CSF gastrointestinal 3/18 - 1 *Campylobacter* spp.	Respiratory (mild rhinitis 7 days before); nontypable *N.meningitidis* in tracheal aspirate in week 3	Respiratory	Respiratory	Respiratory	Respiratory infection treated with amoxicillin and clavulanate two weeks before
Bilateral weakness	Ascending type 15/18; cranial nerve involvement 2/18	Upper extremities with generalization in second week	Asymmetric	No	In addition to anisocoria andptosis	Bilateral paresis of facial nerve and ptosis
Deep tendon reflex	Areflexia 10/18; hyporeflexia 3/18; hyperreflexia 4/18; nomal reflexes 1/18	Decreased	Hyperreflexia	Normal	Decreased, positive plantar extensor response	Decreased
Nadir (days)	Median 7 (range 3-28)	6	2	10	8	10
Protein content CSF analysis (g/L)	Median 0.59 (range 0.35-1.98)	Initial normal; Repeated 3rd week 0.39, next 2.2	Normal	Normal	Normal	0.39
EMG findings	AIDP 11/18; AMAN 4/18; both axonal and demyelinating (equivocal) 2/18	AMAN; inelicitable nerves (musculocutaneous nerve) or very low proxymal CMAP in ulnar nerve and median nerve (0.2-0.4 mV) on upper extremities, absent F waves	CMAP 44 m/s; absent F-waves; absent SNAP; prolonged DL; equivocal	Absent SNAPs; absent F-waves; decreased SNCV; prolonged DL	low distal CMAP; F- wave latency; prolonged DL; equivocal	AIDP; decreased MNCV 36 m/s
Antiganglioside antibodies	Positive in 10/12 (8 had positive anti-GM1; 5 had multiple antibodies, 4 had anti-GD1b, anti-GQ1b IgG). Highly specific MFS antibodies were negative in all patients	Anti-GM1, anti-GD1a, anti-GD1b	Anti-GM1	Anti-GM1,GD1a, anti-GD1b	Negative	Anti-GD1b
Brain and spinal cord MRI	-	Initial normal; repeated 4 weeks after disease showed enhancement of cervical nerve roots	Normal	Normal	Normal	Normal
Therapy	IVIG 10/18; IVIG and steroids 4/18; steroids exclusively 1/18, spontaneous recovery 1/18, NA 2/18	PE 5 courses, IVIG 2 courses; spontaneous recovery	IVIG, early recovery	IVIG and steroids, complete recovery	Complete spontaneous recovery after 3 weeks	Early spontaneous recovery

AIDP = acute inflammatory demyelinating polyneuropathy; AMAN = acute axonal motor neuropathy; anti-GM1/anti-GD1a/anti-GD1b/anti-GQ1b = antiganglioside antibodies; CMAP = compound muscle action potential amplitude; CSF = cerebrospinal fluid; DL = distal latency; EMG = electromyography; GBS = Guillain-Barré syndrome; IF = incomplete form; IVIG = intravenous immunoglobulin; LS = localized subtype; MFS = Miller Fisher syndrome; MNCV = motor nerve conduction velocity; MRI = magnetic reasonance imaging; PCB = pharyngo-cervicobrachial; PE = plasma exchange; SAN = sensory ataxic neuropathy; SNCV = sensory nerve conduction velocity; SNAP = sensory nerv action potential; VZV = varicella zoster virus

DISCUSSION

We observed significant clinical variability and serologic heterogeneity of GBS and its atypical variants, which supported the proposed hypothesis of continuous spectrum of GBS and reconsideration of the existing diagnostic criteria for classic GBS in pediatric population (7,9,13). Literature data on atypical GBS in children are scarce. Our study has demonstrated that atypical variants are not uncommon as we thought, similar to a recent small study (22). Our cohort with typical GBS resembled other populations with Caucasian predominance (Europe, United States, Iran, Japan), showing male predominance and AIDP occcurence as the most common neurophysiologic presentation (17,19,23). Antecedent infection was documented in all patients with atypical variants and half of patients with typical GBS, whereas in the literature it rates up to 60%-70% (4,9,24).The majority of infections remained etiologically unproven. GBS is preceded by *Campylobacter* (most frequently), *M. pneumoniae*, CMV, EBV, Zika or influenza virus infection, and recently SARS-Cov-2 infection (13,25-28). Although GBS has been reported as a postimmunization event, vaccination as a provocative factor in our patients was excluded. GBS following previous immunization (rabies, H1N1 vaccine) is rare (1.6 cases *per* 10^6 vaccinations) and probably it is temporally coincidental rather than causative (13,29-31). In one of our study patients, *Neisseria* was isolated from the upper respiratory tract specimen. Currently, there is insufficient data to confirm a link between GBS and non-typable *Neisseria meningitidis* carrier state (6). Recently, a rare case of MFS after *Neisseria meningitidis* has been reported (32). Nadir is reported to be reached at one week, as we also found in our survey, similar in atypical and typical GBS variants (33).

Antiganglioside antibodies become positive early in the course of disease and are found in around one-third of GBS patients (34). In our survey, around half of the patients with typical GBS and atypical variants had positive antiganglioside antibodies (most commonly anti-GM1). Several types of antibodies are more frequently observed in some GBS variants (13). Up to half of the patients with pharyngocervicobrachial GBS subtype (PCB) have positive IgG anti-GT1a antibodies which often cross-react with GQ1b, whereas patients with Miller Fisher syndrome (MFS) carry mostly IgG anti-GQ1b antibodies which cross-react with GT1a (7). Serologic heterogeneity suggests continuous spectrum of GBS and shows more pathogenetic than clinical notability in the evaluation of GBS patients. Also, antiganglioside antibodies could be involved in a variety of other diseases including other neurological diseases (35). CSF findings usually do not differ between typical GBS and its variants, as found in our survey (36). CSF analysis is normal in up to 50% of patients with GBS during the first week of disease, and shows an increased protein level in most cases when obtained one week after the onset of weakness (1,13). Neuroimaging studies are not routinely used. However, due to unusual presentation, all of our patients with atypical GBS underwent brain MRI scans and were normal except for one patient with enhancement of the cervical nerve roots, which is not specific to GBS and occurs in other inflammatory neuropathies (neuroborreliosis) and even in neurodegenerative disorders (33,37,38).

Short-term outcomes were favorable in typical and atypical variants, leading to achievement of full recovery in most patients. Nonlethal outcome was found. The patient described as case 1 showed signs of autonomic dysfunction which may be life-threatening. Swallowing difficulties, low and nasal voice, neck muscle weakness and low blood oxygen might be early signs of respiratory insufficiency. In case of dysphagia and weak cough, intubation is recommended (4). Posterior reversible encephalopathy syndrome and priapism have been rarely described in adolescents with GBS, being more frequent in adults (39). The clinical course was more severe and prolonged in the patient with descending type of PCB. On the contrary, two patients (age 2 and 5 years) with atypical variant recovered spontaneously due to mild form of disease (GBS disability score 1 and 2). Although IVIG and PE have been reported as equally effective, IVIG is preferred due to practical reasons, and thus more frequently used in case of the loss of ability to walk unassisted (modified Rankin score 4). Corticosteroids are indicated and efficient in up to 80% of patients with disease progression over week 4 toward week 8. Further clinical course could be complicated by development of CIDP (when detection of neurofascin 155 IgG4 antibodies against paranodal proteins is considerable), or by the occurrence of disease fluctuation/clinical impairments related to treatment two weeks after IVIG (40,41).

Previous clinical-serologic studies indicate significant overlap between GBS and MFS variants within the GBS spectrum (7,42). In our study, three patients with atypical GBS showed signs of incomplete MFS forms, whereas one patient showed overlap with PCB, as reported by other authors (26). PCB may have fulminant presentation with tetraplegia and altered consciousness overlapping with brainstem encephalitis or with dysphagia and nasal speech with positive anti-GT1a antibodies as incomplete PCB form. The pattern of neuromuscular weakness in patients with botulism also resembles one in MFS and PCB, possibly because of molecular target carbohydrate residues on gangliosides which serve as receptor for botulinum toxin.

There is an increasing number of reported overlaps between GBS and acute disseminated encephalomyelitis, however, not present in our cohort (28,43). Despite some study limitations (modest sample size, single-center experience, retrospective nature of the present study), we believe that our survey contributes to the respective literature by showing interesting insights into GBS and its atypical variants in children.

CONCLUSION

Clinical spectrum of GBS variants might be more common than previously thought, as they tend to be frequently misdiagnosed. The diagnosis is based on clinical history, examination and investigation of evolved clinical/neurological status, which is heterogeneous. As the spectrum of GBS presents with highly variable, atypical and incomplete clinical manifestations, the existing diagnostic criteria for classic GBS in pediatric population should be reconsidered, as supported by the recently proposed and published diagnostic guidelines. Accurate diagnosis is important for rational and timely treatment.

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S A Ž E T A K

GUILLAIN-BARRÉOV SINDROM I ATIPIČNE VARIJANTE U DJECE: ISKUSTVO TERCIJARNOG CENTRA U REPUBLICI HRVATSKOJ

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Cilj: Prikazati heterogene kliničke značajke inačica atipičnog Guillain-Barréova sindroma (GBS) te preklapanje između različitih GBS tipova i podtipova. ***Metode:*** Retrospektivna analiza podataka koji uključuju neurološke značajke, analizu cerebrospinalne tekućine, rezultate ispitivanja antigangliozidnih protutijela, nalaze elektromiografije (EMG), magnetsku rezonanciju mozga i kralježnice (MRI), svih pedijatrijskih bolesnika liječenih zbog GBS-a u tercijarnom centru u 10-godišnjem razdoblju. ***Rezultati:*** Liječeno je ukupno 23 djece zbog GBS-a. Atipične varijante pronađene su u pet bolesnika i uključivale su bifacijalnu i tešku faringo-cerviko-brahijalnu silaznu slabost, leziju šestog živca popraćenu parestezijama donjih ekstremiteta, senzoričku ataktičnu neuropatiju i leziju facijalnog živca, akutnu ptozu s midrijazom i nepotpunim Miller Fisherovim sindromom te bilateralnu parezu facijalnog živca (sve po jedan slučaj). Inicijalna analiza cerebrospinalne tekućine pokazala je većinom normalnu razinu proteina. Radiološka obrada je bila uredna u svim atipičnim varijantama osim u bolesnika s faringo-cerviko-brahijalnom varijantom gdje je nađen pojačan signal u korijenu živaca cervikalne kralježnice. EMG je prva dva tjedna bolesti pokazao produljenu distalnu latenciju i proksimalni blok u 3/5 bolesnika, gubitak aksona na gornjim ekstremitetima u bolesnika s faringo-cerviko-brahijalnim podtipom te odsutne F-valove i neuronske potencijale u 3/5 bolesnika. Blago smanjenje brzine provođenja u distalnim segmentima živaca bilo je prisutno u 2/5 bolesnika. Antigangliozidna protutijela bila su pozitivna u 4/5 bolesnika. ***Zaključak:*** Kliničke manifestacije GBS-a vrlo su varijabilne, a atipične varijante/preklapanja nisu rijetke. Ovo istraživanje podupire predloženu hipotezu o kontinuiranom spektru GBS-a koja zahtijeva preispitivanje postojećih dijagnostičkih kriterija za klasični GBS u dječjoj populaciji te uključenje kriterija za varijante GBS-a koji su nedavno predloženi i objavljeni.

Ključne riječi: Guillain-Barréov sindrom, polineuropatija, atipične varijante, djeca

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THE ROLE OF SOCIAL SUPPORT IN THE VOICE-SPEECH REHABILITATION PROCESS

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Objective: to investigate the relationship between perceived informal social support and speech therapy parameters including the following: applying instructions given by the speech-language pathologist, success in acquisition of alaryngeal speech, and use of alaryngeal voice in everyday social interactions in laryngectomized patients. ***Methods:*** this retrospective study included 47 laryngectomized males, mean age 67.19 years. Data were collected in a semi-structured interview over the voice-speech therapy duration. The data collected were statistically analyzed in a JASP software (version 0.12.2., University of Amsterdam, The Netherlands) by appropriate statistical methods. ***Results:*** the alaryngeal speech usage in real communication circumstances is positively strongly associated with marital status, social support, following instructions and self-discipline, and successful voice-speech rehabilitation. ***Discussion:*** these findings suggest that informal social support is an important protective factor in rehabilitation process of laryngectomized patients that facilitates acquisition of alaryngeal voice. The results were in concordance with similar research findings indicating association between greater perceived social support and better treatment outcomes. ***Conclusion:*** informal social support has an important role in all components of voice-speech therapy of laryngectomees, where the most important association is with success in learning substitute speech.

Key words: laryngectomy, psychosocial adaptation, social support, speech therapy, voice rehabilitation

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INTRODUCTION

Diagnosis of malignant disease represents a direct threat to one's life and integrity. From the time of receiving a cancer diagnosis, these people are faced with extreme distress accompanied by a wide range of emotional responses that can influence both morbidity and mortality, and as such affect the lives of patients in many ways. Although medical treatment largely depends on the cancer size, stage and site, total laryngectomy is still considered the gold standard and the most common treatment choice in laryngeal malignancies, often followed by neck dissection and chemo-radiotherapy. These highly invasive treatment procedures combined with illness intrusiveness result in multiple permanent debilitating side effects and functional difficulties related to swallowing, chewing, eating and speaking accompanied by chronic pain. Besides these disease-specific challenges, individuals with laryngeal cancer have to face incremental psychosocial stressors common to the majority of cancer patients, such as fear of dying slow, painful death, fear of disability, becoming helpless and dependent on their loved ones, fear of change in appearance and body function, emotional vulnerability, uncertainty, altered social roles, social isolation and embarrassment (1). There is a growing body of literature that highlights the adverse consequences of unmet psychological needs of head and neck cancer patients, most of them leading to the increased length of hospital stay, more treatment complications, increased noncompliance with treatment protocols, higher psychiatric

comorbidities, and suicide risk (2). The effects of mutilating surgical procedures resulting in appearance alterations, changes in voice production, respiratory function, disrupting the structural and functional integrity of this region that is crucial for emotional and social expression lead to a number of psychosocial problems in laryngectomy patients. On this journey of uncertainty about future and dealing with the unpredictable outcomes, there are few factors that have been recognized as important protective determinants of psychosocial adaptation to laryngeal cancer. One of these factors is social support that has been found to facilitate post-treatment adjustment and promote recovery in head and neck cancer patients (3). Caplan *et al*. consider the lack of perceived social support as one of the most significant factors contributing to poor psychosocial adaptation in cancer patients (4). Penedo *et al*. emphasize the importance of perceived social support during treatment and rehabilitation processes in head and neck cancer patients, stating that the lack of perceived social support may be a risk factor for poor post-treatment recovery and adjustment (5). Increasing evidence suggests that a higher level of perceived social support in head and neck cancer patients facilitates post-treatment adjustment and influences disease-specific health-related quality of life (6,7). However, the loss of laryngeal voice and fear of stigmatization due to postoperative disfigurement often result in social isolation of laryngectomees depriving them of social support resources and increasing the risk of developing psychiatric comorbidities. Moreover, these maladaptive patterns may result in making poor health choices, compromise patient compliance with treatment, and interfere with rehabilitation process. Finally, nonadherence to treatment in voice rehabilitation after total laryngectomy prevents proper acquisition of alaryngeal speech, leaving patients with serious communication impairment in social interactions. Post-laryngectomy voice rehabilitation provides three available methods of alaryngeal voice: tracheoesophageal voice by insertion of a tracheoesophageal prosthesis, production of esophageal voice, and use of mechanical generators of acoustic vibrations. Despite these important implications, there is limited research on social support in the population of laryngectomy patients and little is known on how the perceived social support and substitute voice acquisition interact in the rehabilitation process. Kotake *et al*. suggest that social support and acquisition of alternative voice may promote psychological adjustment after laryngectomy through enhancement in self-efficacy and locus of control (8). Social support encourages alaryngeal voice acceptance, which, combined with improvement of speech parameters, increases the probability of using it in various communication situations in daily-life tasks (9). There are two types of social support. Informal social support is defined as support provided outside formal settings (from family, friends, patient associations), while formal support includes support provided by health professionals, paid helpers, or companies that provide caregiving help.

The aim of this retrospective study was to investigate the relationship between perceived informal social support and voice-speech therapy parameters including the following: applying instructions given by the speech-language pathologist, success in acquisition of alaryngeal speech, and use of alaryngeal voice in everyday social interactions in laryngectomized patients.

PATIENTS AND METHODS

The sample consisted of 47 totally laryngectomized males, mean age 67.19 years. Data were collected by use of a retrospective semi-structured interview over the voice-speech therapy duration. Semi-structured interview was conducted targeting the degree of perceived informal social support from different groups of sources, i.e. partners, children, other family members, friends, work colleagues, and other laryngectomized patients. Patients were asked whether or not they felt supported and understood by their close ones and if they received emotional help and support they needed. The effectiveness of voice rehabilitation was assessed on the basis of the Harrison-Robillard-Schultz (HRS) scale for tracheoesophageal speech, Stanković scale for esophageal speech, and auditory-perceptual assessment of the speech intelligibility for electrolaryngeal speech.

The data collected were statistically analyzed in JASP computer program (version 0.12.2., University of Amsterdam, The Netherlands). Categorical variables were statistically expressed as absolute and relative frequencies. Numerical data were expressed as arithmetic mean and standard deviation. Preliminary analyses showed that the assumptions of normality, linearity and homogeneity of variance were not violated. The correlation of numerical variables was estimated by Pearson correlation coefficient r. All p values were two-sided. The level of significance was set at $\alpha=0.05$.

RESULTS

Based on the analysis of the data collected, 47 male respondents, mean age 67.19 years, age range 39-86 years, participated in the research. The majority of subjects, 44 (93.61%) of them, were included in the voice-speech therapy after laryngectomy. According to the level of education, 30 (63.83%) respondents had acquired some education level, whereas 17 (36.17%)

had not completed their education. Psychiatric heredity was recorded in 44 (93.16%) and psychiatric comorbidity in 34 (72.34%) subjects. More than half of the respondents, 31 (65.95%) of them, were in a marital, extramarital or partnership union, whereas 16 (34.04%) respondents had the status of a widower, divorced or unmarried. Thirty-four (72.34%) respondents had informal psychosocial support during medical treatment and voice rehabilitation. During voice-speech therapy, 34 (72.34%) respondents followed the instructions of a speech-language pathologist and regularly performed rehabilitation operators independently at home with formal voice-speech therapy by speech-language pathologist. Thirty-six (76.59%) respondents were successfully rehabilitated regardless of a substitute modality of alaryngeal speech, and 34 of them (94.44%) used alaryngeal speech in everyday real communication circumstances.

Analysis of the results showed a medium positive correlation between psychiatric heredity and psychiatric comorbidity (r=0.42, p=0.003), medium negative correlation between the level of education and perception of informal social support (r=-0.32, p=0.025), and strong positive correlation between marital status and perception of informal social support (r=0.76, p=0.056). There was a strong negative correlation between following instructions and self-discipline and the patient level of education (r=0.52, p=0.543) and strong positive correlation between marital status and following instructions and self-discipline (r=0.66, p=0.256).

A weak negative correlation was found between psychiatric comorbidity and following instructions and self-discipline (r=-0.25, p=0.083) and medium positive correlation between the level of education and success in voice-speech therapy (r=0.42, p=0.003). There was a strong positive correlation between success in voice-speech therapy and marital status (r=0.55, p=0.460), perception of informal social support (r=0.66, p=0.490), and following the instructions and self-discipline (r=0.66, p=0.002). A medium negative correlation was found between the level of education and alaryngeal speech usage in real communication circumstances (r=-0.42, p 0.003). The alaryngeal speech usage in real communication circumstances showed strong positive correlation with marital status (r=0.56, p=0.322), social support (r=0.57, p=0.473), following instructions and self-discipline (r=0.68, p=0.304) and successful voice-speech rehabilitation (r=0.89, p 0.04).

DISCUSSION

In this study, we examined the relationship between perceived informal social support and three parameters of voice rehabilitation in patients after total laryngectomy including following instructions given by the speech-language pathologist, success in acquisition of alaryngeal speech, and use of alaryngeal voice in everyday social interactions. The results indicated positive correlation between perceived informal social support and two important components of voice-speech therapy (following instructions during rehabilitation and success in acquisition of alaryngeal speech), as well as a significant positive association between perceived informal social support and use of alaryngeal voice in everyday communication. These findings suggest that informal social support is an important protective factor in rehabilitation process of laryngectomized patients that facilitates acquisition of alaryngeal voice. The results are in concordance with similar research findings indicating association between greater perceived social support and better treatment outcomes (6). It is possible that this interaction is mediated through good psychological adjustment to illness and treatment since it is well known that social support promotes psychological adjustment of cancer patients (10).

Considering literature findings emphasizing social support seeking as the most frequently used coping strategy in laryngeal cancer patients, it is plausible that increased perceived social support and encouragement provided by the loved ones enhances individual's involvement in treatment resulting in better treatment results. However, since these correlations do not allow causative conclusions, it is possible that the successful alternative voice acquisition promotes patient perception of better social involvement and support. Non-significant relationship between perceived informal social support and following instructions given by the speech-language pathologist and alaryngeal speech usage in this specific male sample could be explained by a study showing that perceived informal social support was not significantly related to psychosocial adjustment of men (7). This finding might also be due to a relatively small patient sample. The research also yielded a statistically significant correlation between successful acquisition of alaryngeal speech and the alaryngeal voice usage. This association could be explained by the fact that patients who successfully acquired alaryngeal speech were frequently encouraged by the speech-language pathologist to practice it in everyday situations. Furthermore, we found a significant positive correlation between marital status and perceived informal social support. These findings are supported by a study claiming positive correlation between social support from family member and physical and psychological adjustment to cancer (11). Finally, this study found a significant positive correlation between educational level and successful alaryngeal voice acquisition. It is possible that this finding

could be explained through the mediating process of self-efficacy. Namely, research in this field claim a strong positive association between the level of education and perceived self- efficacy (12).

The limitations of this study included a relatively small sample that limited the power of conclusions about investigated relationships. The lack of sex diversity prevents extrapolation of the results to all laryngectomized patients in voice therapy. Furthermore, the data presented were strictly correlational and did not include causal associations between perceived social support and parameters of voice rehabilitation. Finally, there was a lack of standardized measures of the observed and reported parameters in the study. Although there are several assessment tools to assess social support in adults, there is a lack of instruments for measuring the concept of informal social support in clinical settings. The use of standardized questionnaires would provide more reliable and objective measurements and enable comparison of the results with those in other cancer patients, as well as those in the general population. A key strength of the present study was that it provided valuable information on the potential role of informal social support in the course and outcomes of voice-speech therapy, which is considered a vital part of rehabilitation of laryngectomees. Study results could facilitate rehabilitation and promote recovery of laryngectomized patients.

CONCLUSION

Social support has an important role in all components of voice-speech therapy of laryngectomized persons, with a statistically significant association between social support and success in substitute speech learning, as well as between alaryngeal speech usage in real communication circumstances and successful voice-speech rehabilitation.

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SAŽETAK

ULOGA SOCIJALNE PODRŠKE U PROCESU GLASOVNO-GOVORNE REHABILITACIJE

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Cilj **ove studije bio je istražiti odnos između percipirane neformalne socijalne potpore i bitnih sastavnica logopedske terapije, uključujući samostalno provođenje rehabilitacijskih operatora prema uputama logopeda, uspješno usvajanje i upotreba alaringealnog glasa i govora u svakodnevnim socijalnim interakcijama kod laringektomiranih osoba.** ***Metode:*** **Retrospektivna studija obuhvatila je 47 laringektomiranih muškaraca srednje dobi 67,19 godina. Podatci su prikupljeni polustrukturiranim intervjuom tijekom trajanja glasovno-govorne terapije. Prikupljeni podatci statistički su analizirani u računalnom programu JASP (verzija 0.12.2., Sveučilište u Amsterdamu, Nizozemska) odgovarajućim statističkim metodama.** ***Rezultati:*** **Upotreba alaringealnog govora u stvarnim komunikacijskim okolnostima pozitivno je snažno povezana s bračnim statusom, socijalnom potporom, samodisciplinom laringektomiranih tijekom terapije i uspješnom glasovno-govornom rehabilitacijom.** ***Rasprava:*** **Dobiveni rezultati ukazuju na to da je neformalna socijalna potpora važan zaštitni čimbenik u procesu rehabilitacije laringektomiranih osoba, koji olakšava proces rehabilitacije. Rezultati su sukladni rezultatima sličnih istraživanja koji ukazuju na povezanost veće percipirane socijalne potpore i boljih rezultata liječenja.** ***Zaključak:*** **Neformalna socijalna potpora ima važnu ulogu u svim sastavnicama glasovno-govorne terapije laringektomiranih, pri čemu je značajnija povezanost socijalne potpore s uspješnim usvajanjem alaringealnog glasa i govora.**

Ključne riječi: **laringektomija, psihosocijalna prilagodba, socijalna potpora, logopedska terapija, glasovna rehabilitacija**

COVID-19 REINFECTION IN A PATIENT WITH END-STAGE RENAL DISEASE ON CHRONIC HEMODIALYSIS: IS IT POSSIBLE OR IS IT INACCURACY OF TESTING?

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Patients with end-stage renal disease (ESRD) on hemodialysis (HD) are at a high risk of acquiring SARS-CoV-2 and of developing severe COVID-19 and death. The possibility of being reinfected with this virus is poorly understood. To date, there are a small number of reports of reinfections in COVID-19 patients, especially in HD patients, with only four cases described so far. The aim was to show the possibility of reinfection and developing severe acute respiratory syndrome in HD patients. We describe a 69-year-old ESRD patient who had been on HD treatment for three years, with diabetes mellitus and a history of ischemic cardiomyopathy. The patient was tested for SARS-CoV-2 by a nasopharyngeal polymerase chain reaction (PCR) test because of a positive cluster at his dialysis unit and initially diagnosed with COVID-19 in July 2020. In this period, he had mild symptoms for a few days and remained asymptomatic afterwards. Four months later, he presented to the hospital with fatigue, high fever and shortness of breath, and was COVID-19 positive again. This case points to the possibility of reinfection, lack of immune response after an asymptomatic or mild infection, or even the possibility of the first false-positive PCR test. Future longitudinal studies are needed to evaluate the potential reinfections, recurrence, and duration of antibody detection.

Key words: chronic kidney disease, hemodialysis, COVID-19 reinfection

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INTRODUCTION

In December 31, 2019, the World Health Organization (WHO) China country office notified of the cases of pneumonia of unknown etiology detected in Wuhan city, Hubei province, with subsequent detection of a new strain of coronavirus on January 7, 2020. The virus was subsequently named by the WHO as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by it as COVID-19. COVID-19 has evolved into a global pandemic as declared by the WHO on March 11, 2020 (1), and caused over 15 million infections and half a million deaths worldwide (2).

Patients with chronic kidney disease (CKD) and those on renal replacement therapies are potentially susceptible to developing COVID-19 infection, given the concentration of the risk factors and comorbidities (3). Patients on chronic hemodialysis (HD) have a high risk of both infection and severe disease because of their fragility and unavoidable health care-related contacts. The diagnosis may be challenging; false-negatives are frequent, and persistence of positivity may be prolonged (4).

CASE REPORT

We report on a 69-year-old-man on chronic HD due to diabetes nephropathy, with a history of ischemic cardiomyopathy and implanted bypass due to a three-vessel coronary heart disease.

He was screened because of a positive cluster in his dialysis unit. He was found positive for SARS-CoV-2 by a nasopharyngeal polymerase chain reaction (PCR) test on July 22, 2020. The patient was isolated and ambulatory dialyzed in a special COVID unit. Except for fatigue, the patient did not report any other symptoms for several days. On the first physical examination, he was afebrile and hemodynamically stable (blood pressure 120/70 and heart rate 89 beats/minute) with oxygen saturation of 98%. Auscultatory finding on the lungs was normal. Complete blood count revealed normal findings, with the exception of thrombocytopenia, which had been present before (Le $6.1x10^9$, Er $4.59x10^{12}$, Hgb 144 g/l, Plt $91x10^9$) and normal values of C-reactive protein (CRP; 5 mg/mL). His chest x-ray showed a congestive state, which could not completely rule out incipient infiltrative changes and he was administered antibiotic therapy with azithromycin 500 mg for six days. He continued with HD every other day and was regularly monitored by a nephrologist. During this period, the patient was feeling well and was clinically stable. He tested negative on August 3, 2020 and his isolation measures were discontinued.

On November 11, 2020, the patient's daughter called his dialysis unit to inform that her father was febrile and felt fatigue with occasional vomiting. The patient had a PCR test, which came back positive. On physical examination, he was febrile and dyspneic with oxygen saturation of 93%, and bilateral basal crackles were heard on the lungs. The blood count was similar to the previous one but increased CRP levels were noticed (>120 mg/mL). Now his chest x-ray showed congestive changes and bilateral infiltration. He continued his ambulatory HD treatment in the COVID positive unit and there he received antibiotic treatment with cephazolin 2 g intravenously (i.v.), but he still felt unwell. On day 9 of illness, after HD he worsened, could not breathe, and had severe dyspnea with oxygen saturation of 75% and limb cyanosis. He was urgently transported to the COVID Disease Isolation Center. Upon arrival, his clinical state worsened with a very low oxygen saturation of 42% and he was immediately placed on oxygenation. His blood count and CRP were the same with azotemia (urea 29.2 mmol/L, creatinine 899 μmol/L), electrolyte imbalance (Na 128 mmol/L, K 5.7 mmol/l, Cl 101 mmol/L), very high values of D-dimer (36.5 mg/L) and immeasurable fibrinogen. Native computed tomography scan (CT) of the thoracic organs showed extensive ground glass opacities (GGO) and gentle consolidation of the peripheral and basal parts of the lungs. He was administered dexamethasone 6 mg i.v., ceftriaxone 2 g i.v., doxycycline cps 2x100 mg *per os* daily, and low molecular weight heparin 40 mg twice a day, in addition to the patient's chronic therapy. The patient was also on CVVHD treatment according to the protocol and under oxygenation up to 6 L/min. When the PCR test came negative a few days later, he was transferred to the Nephrology Department, where his laboratory findings were similar to those mentioned above, with high LDH level (1098 U/L) and a decrease in CRP (94.4 -57.7 mg/L), D-dimer (8.05 mg/L) and fibrinogen (2.1 g/L) values. Control CT showed significant regression of the previously observed changes. Serologic testing showed an IgG level of 91.4600 AU/mL and IgM of 14.7200 AU/mL.

With the given therapy and regular HD treatment, the patient gradually recovered but still was weak, hypotensive, and cardiopulmonary compensated. Upon discharge, he continued HD in his unit, but his overall condition worsened compared to the condition before the infection, when he was a clinically stable patient.

DISCUSSION

To the best of our knowledge, only four cases of COVID-19 reinfection in HD patients have been reported. Mendoza *et al.* (5) presented a case of a clinically manifest infection that followed two months after detecting low IgG antibody with a negative PCR test. Krishna *et al.* (6) described two patients with suspected recurrent COVID-19 infection, each with documented clearance of virus between the episodes. In these two patients, the time elapsed between the negative reverse-transcription PCR test result for SARS CoV-2 and symptomatic reinfection was 31 and 55 days, respectively. Both of these patients were tested after a contact with a positive person and had no symptoms; then, one patient had severe symptoms and required hospitalization, whereas the other had mild symptoms and was treated as outpatient (6).

In addition, Torreggiani *et al.* (4) report on a patient who was screened because of a positive cluster in his nursing home and tested PCR positive; 22 days after testing negative, he developed fever and bilateral pneumonia. In this case, besides reinfection, the authors highly suspected the occurrence of virus reactivation and inaccuracy of testing (4).

In our case, we could not rule out the possibility of the initial false-positive test either. It was quite unlikely because the patient lived in a city that recorded a large number of infected inhabitants and also had a suspicious contact in his HD unit.

The PCR tests for SARS-CoV-2 detection are considered as the gold standard but are not perfect, especially in clinical practice because false tests can have fatal consequences (7). Technical problems including con-

tamination during the sampling and cross-reactions with other viruses or genetic material may be responsible for false-positive results. When interpreting the results, it is important to consider the patient epidemiologic history and previous COVID-19 disease. When there is a low probability based on all these data, a positive result should be interpreted with caution and another test should be performed (8).

In our case, additional test was not performed after the first positive PCR test because our patient had a positive epidemiologic survey.

Reinfections with other human coronaviruses can occur, while reinfection with SARS-CoV-2 in humans is rare and unknown (9). Selvaraj *et al*. presented a number of 34 reinfections recorded worldwide until November 2020 (10). Most people infected with SARS-CoV-2 have detectable antibodies for 10-14 days of symptom onset, while antibody titer is low or even impossible to detect in patients with a mild clinical picture (11). There is little information about the strength and length of protection provided by this immune response against future infections (10). One Chinese study showed 40% of asymptomatic cases and 12.9% of symptomatic patients who became seronegative in the early convalescent phase (8 weeks after infection) (12). Whether these findings of the presence of SARS-CoV-2 antibodies in patients with CKD is similar to the general population is still unknown (13).

In our case, no serologic testing was performed after the first positive test, which is a limitation of our report, and we do not know whether the patient developed antibodies after the initial infection or became seronegative after a certain period. After the second infection, serologic testing showed a high amount of both IgG and IgM antibodies. This goes in favor to the fact that infections with mild symptoms have lower antibodies and is more likely to get reinfected (10). But, opposite to our case where reinfection presented with severe symptoms, most infections with respiratory viruses occur with milder symptoms due to a stronger immune system response that can occur when reinfection occurs with a different strain of the same virus (14).

This case presents the possibility of reinfection, lack of immune response after mild symptoms, or even an initial false-positive test. Based on the previously reported cases of reinfection, it is indicative that the immunity developed after COVID-19 infection cannot provide lifetime protection. There is also a paradox between the decrease in antibody titer that occurs over time and the low incidence of reinfections, which points to complex immune mechanisms. In order to better understand those mechanisms, longitudinal studies in the future are needed, as well as a uniform diagnostic approach to the patient, which will allow better comparison of patients from different hospitals and countries.

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SAŽETAK

PONOVNA INFEKCIJA COVID-19 U BOLESNIKA SA ZAVRŠNIM STADIJEM KRONIČNE BOLESTI BUBREGA NA KRONIČNOJ HEMODIJALIZI: JE LI TO MOGUĆE ILI SE RADI O DIJAGNOSTIČKOM PROPUSTU?

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Bolesnici s terminalnom bubrežnom bolešću koji su na hemodijalizi (HD) pod visokim su rizikom od zaraze virusom SARS-CoV-2 i od razvijanja teške kliničke slike bolesti COVID-19. Mogućnost ponovne zaraze ovim virusom još je uvijek većinom nepoznata. Do danas je opisan manji broj COVID-19 reinfekcija, pogotovo kod bolesnika na HD gdje su dosad opisana samo četiri slučaja. Prikazujemo mogućnost reinfekcije virusom SARS-CoV-2 i razvoja teškog akutnog respiracijskog sindroma kod bolesnika na HD. *Prikaz bolesnika:* Bolesnik u dobi od 69 godina je na kroničnom programu HD tri godine zbog bubrežnog zatajenja tijekom dijabetičke nefropatije s anamnezom ishemijske kardiomiopatije te dvostrukim CABG zbog trožilne koronarne bolesti. U srpnju 2020. godine bolesnik je testiran pozitivno metodom PCR na SARS-CoV-2 zbog kontakta s pozitivnim bolesnikom u zajedničkom prijevozu na dijalizu. U tom je razdoblju imao blage simptome, umor nekoliko dana, nakon čega je postao asimptomatičan. Nakon četiri mjeseca javlja se u bolnicu s visokom tjelesnom temperaturom, teškom zaduhom i lošim općim stanjem te je opet COVID-19 pozitivan. *Zaključak:* Ovaj slučaj ukazuje na mogućnost reinfekcije, slabog imunosnog odgovora nakon asimptomske ili blage infekcije ili čak prvog lažno pozitivnog PCR testa. Da bi se evaluirao potencijalni mehanizam reinfekcija, eventualnih recidiva i trajanje imunosnog odgovora potrebne su buduće longitudinalne studije.

Ključne riječi: kronična bubrežna bolest, hemodijaliza, reinfekcija COVID-19

KAMPTOKORMIJA I MIOTONIČNA DISTROFIJA TIP 2

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Prikazujemo rijedak slučaj sekundarne kamptokormije u pacijentice s miotoničnom distrofijom tip 2. Dijagnoza kamptokormije temelji se na kliničkom zapažanju abnormalne antefleksije trupa (>45°) u stojećem položaju, koja se pogoršava pri hodanju, a smanjuje u ležećem položaju. Dijagnoza miotonične distrofije tip 2 temelji se na kliničkoj slici proksimalne miopatije, tipičnom elektromiografskom nalazu i neuroradiološkoj obradi kralježnice (MSCT/MR), a potvrđuje se DNA analizom. Postoje brojni uzroci sekundarne kamptokormije, a miotonična distrofija tip 2 je jedan od rjeđih. Hipotrofija/atrofija paravevertebralne muskulature pri čemu je mišićno tkivo nadomješteno masnim tkivom, verificirana neuroslikovnim metodama, upućuje na potrebu za dodatnom obradom s ciljem isključenja različitih mišićnih bolesti i poremećaja. Ovaj slučaj zorno prikazuje da u pozadini kroničnih, bolnih, vertebrogenih sindroma ponekad egzistiraju puno kompleksnije i rjeđe bolesti.

Ključne riječi: kamptokormija, miotonična distrofija, elektromiografija

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UVOD

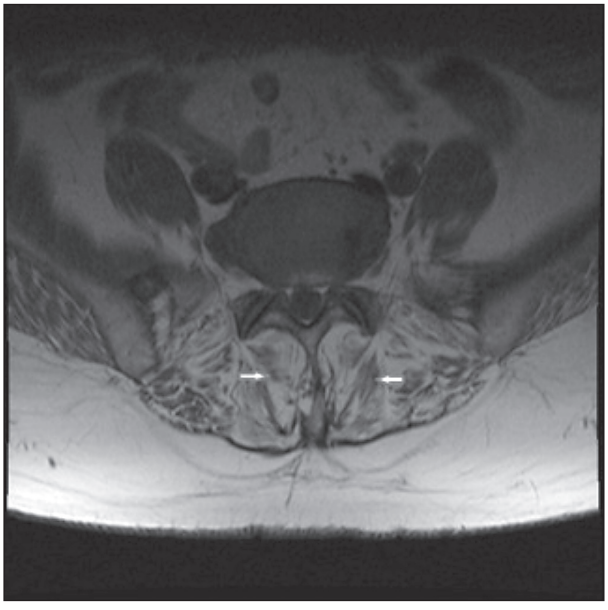
Prikazujemo rijedak slučaj sekundarne kamptokormije u pacijentice s miotoničnom distrofijom tip 2 (MD2). Dijagnoza kamptokormije temelji se na kliničkom zapažanju abnormalne antefleksije trupa (>45°) u stojećem položaju, koja se pogoršava pri hodanju, a smanjuje u ležećem položaju (1).

Dijagnoza MD2 temelji se na kliničkoj slici proksimalne miopatije, tipičnom elektromiografskom (EMG) nalazu i neuroradiološkoj obradi kralježnice (MSCT/MR), a potvrđuje se DNA analizom (2). Postoje brojni uzroci sekundarne kamptokormije, a MD2 je jedan od rjeđih.

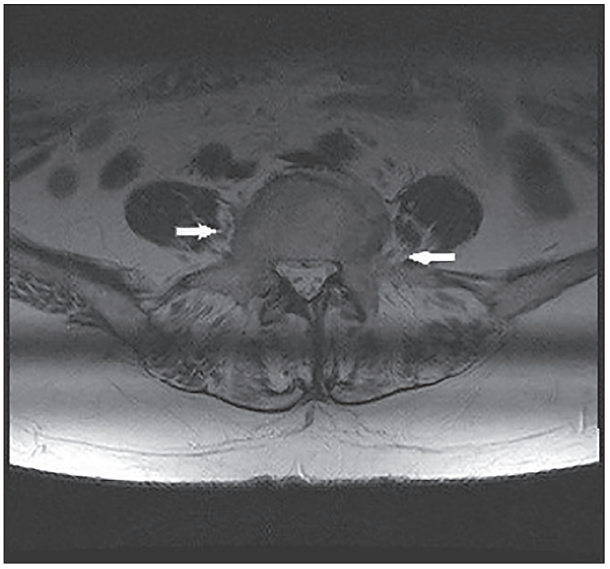
PRIKAZ BOLESNICE

Pacijentica u dobi od 68 godina hospitalizirana je zbog bolova u torakolumbalnom dijelu kralježnice zadnje dvije godine. Anamnestički, operirala je mrenu na lijevom oku u 45. godini života. U vanjskoj ustanovi napravljena je elektromioneurografija (EMNG) te je dijagnosticirana umjerena, kronična, kompresivna retikulopatija L5 obostrano te blaža S1 obostrano. Pri prijmu se neurološkim pregledom utvrdi sljedeće: uredna funkcija kranijskih živaca, meningealni znakovi su negativni, bez šumova nad karotidnim arterijama. Registrira se blaža slabost proksimalne muskulature ramenog i zdjeličnog obruča (MRS 4/5) i pozitivan Gowersov znak. Tonus i osjet na ekstremitetima su uredni. Miotatski refleksi su simetrični, atenuirani, 2+. Babinskijev i Lasegueov znak su negativni. Koordinacija i kontrola sfinktera su uredni. Trup je anteflektiran (doima se kao antalgično držanje). Fleksijske kretnje lumbosakralnim segmentom kralježnice su bolne i reducirane, uz perkusijsku osjetljivost torakolumbalnog prijelaza. Prisutna je torakalna dekstrokonveksna kifoskolioza. Nalazi laboratorijske obrade (hematologija, koagulogram, reumatski testovi, imunološka obrada) su uredni. Uredni su i rezultati biokemijskih pretraga s iznimkom CK 185 U/L (<177). Uredni su nalazi hormona štitnjače i tumorskih biljega (CEA, CA 125, CA 19-9, CA 15-3, CYFRA 21-1, AFP). Uredan je nalaz EKG-a, RDG torakalnih organa, mamografija i ultra-

zvuk abdomena. RDG torakalne i lumbosakralne kralježnice pokazuje umjerene spondilotske i spondiloartrotske promjene, RDG zdjelice s kukovima umjerenu koksartrozu, a denzitometrija osteopeniju. MSCT lumbosakralne kralježnice pokazao je ispupčenje (*bulging)* na razini L2-L3, a u segmentu L4-L5 masivniji disk spondilofit kompleks dorzomedijalno i desno koji za oko 5 mm prominira u kralježnični kanal. U navedenom segmentu izražena je diskartroza s vakuum fenomenom i ventralnim osteofitima. U segmentu L5-S1 vidljiva je manja dorzomedijalna protruzija od 3 mm. Na temelju rezultata navedene obrade postavljene su dijagnoze kroničnog torakalnog i lumbosakralnog sindroma, dekstrokonveksne torakalne kifoskolioze, ispupčenja (*bulging*) diska L2-L3, spondiloze L4-L5 i L5-S1 segmenata, te L5(S1) kronične radikulopatije. Planira se otpust pacijentice uz preporuku analgetske i fizikalne terapije. Neposredno prije otpusta zamijećeno je da se stupanj antefleksije trupa kod pacijentice povećava pri hodanju te se postavi dijagnoza kamptokormije. S obzirom na navedeno odlučili smo se za dodatnu obradu. Napravi se kontrolni EMNG ruku i nogu koji ukazuje na proksimalnu i paravertebralnu miopatiju uz miotonična izbijanja u torakalnim paraverteberalnim mišićima. MR torakalne kralježnice pokazao je naglašenu kifozu, a MR lumbosakralne kralježnice degenerativne promjene drugog stupnja prema Modicu u segmentu L4-L5, manje ventralne i lateralne osteofite u segmentima L1-L2, L2-L3 i L4-L5, te manje dorzalne osteofite u segmentima L2-L3 i L4-L5.



Sl. 1. *MR lumbosakralne kralježnice – transverzalni presjek – atrofija i masna degeneracija paravertebralnih mišića (označeno strjelicom)*



Sl. 2. *MR lumbosakralne kralježnice – transverzalni presjek – atrofija i masna degeneracija oba mišića psoasa (označeno strjelicom)*

U razini L1-L2, L2-L3 i L3-L4 segmenata nalazi se *bulging* diskova, a u razini L5-S1 segmenta manja subligamentna hernija diska (za oko 3,8 mm u ap smjeru) dorzomedijalno i obostrano paramedijalno. Paravertebralna muskulatura u području torakalne i lumbosakralne kralježnice kao i oba mišića psoasa pokazuje znakove atrofije i masne degeneracije (sl.1 i 2). Antitijela na miasteniju gravis su negativna (ani-N-AChR i anti-MuSK). Testiranje na Pompeovu bolest je negativno. DNA analiza na miotoničnu distrofiju tip 1 (MD1) je negativna, a DNA analiza na MD2 pozitivna. Utvrđen je povećan broj tetrapleta citozin-citozin-timin-gvanozin (CCTG) u „*cellular nucleic acid-binding protein*" (CNBP) genu. Obiteljska anamneza pacijentice na MD je negativna (roditelji preminuli, nema braće i sestara ni potomstva). Oftalmološkim pregledom verificira se katarakta na desnom oku. Rezultati kardiološke obrade (holter-EKG, ultrazvuk srca) su u granicama normale. Nakon kompletiranja rezultata obrade postavljene su dijagnoze MD2 i sekundarne kamptokormije.

RASPRAVA

MD je autosomno dominantna mišićna bolest karakterizirana miotonijom i mišićnom disfunkcijom. Prevalencija se procjenjuje na 5-10/100.000. MD2 je slična no blaža multisistemska bolest od MD1 i kod nje su češće katarakta, intolerancija glukoze/dijabetes te kardiomiopatija (3). MD2 je rezultat povećanog broja ponavljanja tetrapleta CCTG u nekodirajućoj regiji gena CNBP na kromosomu 3. MD2 oboljeli imaju od 75 do više od 11 000 CCTG ponavljanja. Ekspandirani CCTG tetraplet kod oboljelih od MD2 nalazi se u intronu 1 gena CNBP i transkribira se u RNA, ali se

ne translatira u protein. Mutirani gen CNBP proizvodi promijenjeni oblik mRNA koji uzrokuje interefenciju proizvodnje mnogih drugih proteina što sprječava mišićne stanice i stanice drugih tkiva u normalnom funkcioniranju (4). MD2 je sporo progresivna bolest, kasnog početka, koja se klinički manifestira slabošću proksimalne muskulature, miotonijom, kataraktom, ali i znacima afekcije drugih organskih sustava. Naša pacijentica imala je sljedeće kliničke karakteristike MD2: proksimalnu miopatiju, miotoniju (registriranu EMG-om, bez kliničkih znakova) i kataraktu (stanje nakon operacije katarakte lijevog oka te novodijagnosticiranu kataraktu desnog oka). Također, kod naše pacijentice nisu registrirani dijabetes ni kardiološke bolesti (kardiomiopatija, smetnje provođenja). Termin kamptokormija je grčkog podrijetla (grč. "camptos"– savijen; "kormos" – trup) i njime se označava abnormalna fleksija trupa (>45°) u stojećem položaju, koja se pogoršava pri hodanju, a smanjuje u ležećem položaju (za razliku od Parkinsonove bolesti kod koje antefleksija trupa ne regredira u ležećem položaju te je pozitivan fenomen "nevidljivog jastuka" – pri čemu je glava pacijenta zbog rigora odignuta od podloge) (5,6). Razlikujemo primarnu (idiopatsku) i sekundarnu kamptokormiju. Primarna se češće vidi kod žena i starijih osoba s pozitivnom obiteljskom anamnezom i nastaje kao posljedica progresivne slabosti paravertebralne muskulature, dok je ostali neurološki nalaz uredan. Što se tiče sekundarne kamptokormije, obradom je potrebno isključiti: amiotrofičnu lateralnu sklerozu, miasteniju gravis, Parkinsonovu bolest, distoniju, multiplu sistemsku atrofiju, Alzheimerovu demenciju, kroničnu upalnu demijelinizacijsku polineuropatiju, MD1, MD2, aksijalnu miopatiju, disferlinopatiju, nemalinsku miopatiju, mitohondrijsku miopatiju, miopatiju zbog hipotireoze, polimiozitis, dermatomiozitis, fokalni miozitis, miozitis s inkluzijskim tjelešcima, facioskapularnu mišićnu distrofiju, traumu, artritis, hernijaciju i.v. diska te jatrogene uzroke kao što su terapija olanzapinom, donepezilom, valproatom i kortikosteroidima (2,7,8). Uzroci ovog poremećaja mogu biti i psihogeni kao što su histerija, konverzivni poremećaji ili Gilles de la Tourettov sindrom (2,9). Kamptokormija se kao simptom MD2 rijetko spominje u literaturi. Dupeyron i sur. su opisali slučaj 54-godišnje pacijenice s kamptokormijom i MD1 (10). Lawson i sur. su opisali 2 slučaja kamptokormije („*bent spine*" sindrom) kao ranu manifestaciju MD1 (11). Karaahmet i sur. su opisali slučaj kamptokormije u pacijenta s ankilozirajućim spondilitisom i MD (12). Dijagnoza MD2 postavlja se na temelju kliničke slike proksimalne miopatije, tipičnog EMG nalaza (miopatski uzorak u proksimalnoj muskulaturi, uz miotona izbijanja - salve akcijskih potencijala fibrilacijskog tipa trajanja od nekoliko sekundi, promjenjive frekvencije 50-150 Hz i promjenjive amplitude krešendo ili dekrešendo tipa) i neuroradiološke obrade (MSCT/MR kralježnice), a potvrđuje se DNA analizom (13). Hipotrofija/atrofija paravertebralne muskulature pri čemu je mišićno tkivo nadomješteno masnim tkivom, verificirana MR-om, mora biti putokaz za daljnju obradu ponajprije s ciljem isključenja različitih mišićnih bolesti i poremećaja, a prema naprijed navedenim diferencijalno dijagnostičkim mogućnostima (1,2). Moguće terapijske opcije za kamptokormiju uključuju primjenu psihoterapije, fizioterapije, ortoza za kralježnicu, levodope, kortikosteroida, imunoglobulina, ciklosporina, botulinus toksina kao i invazivne zahvate poput stimulacije subtalamičke jezgre ili ortopedske zahvate na kralježnici (2).

Križobolja je veliki zdravstveni i socio-ekonomski problem. Iako se najčešće pripisuje poremećajima intervertebralnih diskova, ne smije se zaboraviti da je diferencijalna dijagnostika križobolje vrlo raznolika te se etiološki može podijeliti na: a) diskogenu (*bulging*, protruzija, prolaps, ekstruzija intervertebralnog diska), b) mišićno-zglobno-koštanu (difuzna idiopatska hiperostotska spondiloza, lumbalna spinalna stenoza, spondilolisteza, spondiloliza, prijelazni kralježak, sindrom m. piriformisa, psoas bursitis, spina bifida okulta, ankilozantni spondilitis, psorijatički artritis, Reiterov sindrom, Pottova bolest, spondiloartritis povezan s upalnim bolestima crijeva, septički spondilitis, fibromialgija, polimialgija reumatika, posturalna križobolja, kifoza i skolioza), c) križobolju uzrokovanu traumom, osteroporotskim frakturama ili tumorima, d) somatsku (uzrokovanu infektološkim – hepatitis C, herpes zoster; ginekološkim – menstrualna bol, lejomiom uterusa, endometrioza, karcinom cerviksa uterusa, trudnoća, upala u području male zdjelice; gastrointestinalni – peptički ulkus, tumori želuca, pankreatitis, tumori gušterače, žučni kamenci, divertikulitis, kolitis, kolorektalni karcinom; urološkim – nefrolitijaza, pijelonefritis, karcinom bubrega, tromboza renalne arterije i vene, prostatitis, karcinom prostate; i vaskularnim poremećajima – aneurizma abdominalne aorte, ateroskleroza), e) križobolju uzrokovanu rjeđim neurološkim poremećajima i uzrocima (sindrom ukočene osobe, Parkinsonova bolest, von Reclinghausenova neurofibromatoza tip 2, Guillain-Barreov sindrom, postpunkcijska), te f) psihogenu križobolju (14,15). Kada se neuroradiološkom obradom kralježnice eliminira diskogena i mišićno-koštano-zglobna križobolja kao najčešća, indicirana je dodatna ekstenzivna obrada s ciljem utvrđivanja njene etiologije.

ZAKLJUČAK

Iako rijetka, ova kombinacija MD2 i sekundarne kamptokormije ukazuje da u pozadini kroničnih, bolnih, vertebrogenih sindroma, a s takvim pacijentima se svakodnevno susrećemo u kliničkoj praksi, pone-

kad mogu egzistirati puno kompleksnije i rjeđe bolesti dijagnosticiranje kojih ispunjava kliničara zadovoljstvom, iako za te bolesti, nažalost, nema učinkovite terapije.

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SUMMARY

CAMPTOCORMIA AND MYOTONIC DYSTROPHY TYPE 2

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We present a rare case of secondary camptocormia in a patient with myotonic dystrophy type 2. The diagnosis of camptocormia is based on clinical observation of abnormal torso anteflexion (>45°) in standing position, which worsens with walking and decreases in supine position. The diagnosis of myotonic dystrophy type 2 is based on the clinical picture of proximal myopathy, typical electromyographic findings, and neuroradiological examination of the spine (MSCT/MR), and is confirmed by DNA analysis. There are a number of causes of secondary camptocormia, and myotonic dystrophy type 2 is one of the rarer ones. Hypotrophy/atrophy of the paravertebral musculature, where the muscle tissue is replaced with fat tissue, verified by neuroimaging methods, indicates the need for additional processing to exclude various muscle diseases and disorders. This case clearly shows that in the background of chronic, painful, vertebrogenic syndromes, much more complex and rare diseases sometimes exist.

Key words: **camptocormia, myotonic dystrophy, electromyography**

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Opće napomene

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