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"CLINICAL LABORATORY PROFESSIONALS NEED THEIR INDIVIDUAL IDENTITY AND LICENSING LIKE OTHER PROFESSIONALS IN THE FIELD OF MEDICINE?"

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Clinical chemistry laboratories have become centres of High-tech Health Care. With modernisation and an explosion of knowledge, there is a great demand for efficiency, quality assurance and timely delivery of results for the benefit of the health of the patient. Genetic screening and nanotechnology also influence the practice of laboratory science. Therefore, a separate code of ethics and guidelines needs to be marked for this area of great potential. [1-2] There is also a need for creating a safeguard within the profession by developing a system for licensing its practitioners. In this paper, we sought to analyse the role of clinical chemistry laboratories in health care and therefore the need to regulate their performance at technical and ethical levels.

Tests performed in clinical laboratories play an essential role in the detection, diagnosis, treatment and prognosis of diseases. These tests are performed by clinical laboratory professionals. Therefore, clinical laboratory science is a profession that:

(a) is distinct from the practice of medicine;

(b) is characterised by its own, internally defined Body of Knowledge and Scope of Practice;

(c) certifies its own practitioners and

(d) requires of its practitioners competency in scientific, technical, managerial and scholarly principles and high standards of performance and professional conduct.[1-2]

The profession of clinical laboratory science includes the design, performance, evaluation, reporting, interpretation and provision of clinical correlations of clinical laboratory testing and the management of all aspects of these services. It is a profession of its own standing that plays a vital role in the field of medicine.

Clinical laboratory tests are utilised for the purpose of diagnosis, treatment monitoring and prevention of disease. The profession includes generalists as well as individuals qualified in a number of specialised areas of expertise, including microbiology/virology, haematology, immunology, transfusion medicine, clinical chemistry, endocrinology, toxicology, cytogenetics and molecular diagnostics. Integral features of each of the specialties may include research, consultation, education, information management, marketing and administration. The profession has a code of ethics that sets forth the principles and standards by which clinical laboratory professionals practice.[1]

As members of the health care delivery team, clinical laboratory personnel are responsible for ensuring reliable and accurate laboratory test results, which contribute to the diagnosis, treatment, prognosis, and prevention of physiological and pathological conditions in humans.

Quality clinical laboratory testing is evidenced by the following: performing the correct test on the right person at the right time, as well as producing accurate test results with the best outcome in the most cost-effective manner. This is accomplished by:

A. Ensuring that appropriate laboratory tests are ordered.
B. Procuring laboratory test samples in an efficient, timely manner.
C. Producing accurate laboratory test results.
D. Correlating and interpreting laboratory test data.
E. Disseminating laboratory test information to clinicians and patients in a timely manner.
F. Evaluating the outcome of clinical laboratory testing for each individual patient and the entire health care system.

THE PRACTICE OF CLINICAL LABORATORY SCIENCE REQUIRES:

A. Assessing, designing, evaluating and implementing new laboratory test methods.
B. Evaluating the appropriateness of existing and new laboratory methods for clinical utility, cost-effectiveness and cost-benefit analysis.
C. Developing, implementing, and reporting results of clinical laboratory services research (i.e., within the context of cost, quality, and access).
D. Designing and implementing cost-effective delivery models for clinical laboratories, including their services and personnel.
E. Developing and implementing a comprehensive Quality Management System to include:

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1. quality control and assurance of clinical laboratory testing services;
2. competency assessment of personnel;
3. integration with other aspects of the health care delivery system for ensuring appropriate utilisation of clinical laboratory testing services.
4. continuous process improvement activities to maximise human resources.

F. Designing, implementing and evaluating the education of new clinical laboratory personnel and the continued education, development and career growth of clinical laboratory professionals.

G. Promoting awareness and understanding of the use of the clinical laboratory.

Description of Current Practice

The following scenarios describe specific examples of the scope of practice within clinical laboratory science.

Providers of Clinical Laboratory Services, upon Either Physician or Consumer Request, in Facilities, which may be Owned or Operated by Clinical Laboratory Scientists

Within the scope of governing the profession, and consistent with ethical and legal considerations, clinical laboratory scientists who are qualified by education and experience perform laboratory tests and provide test results to physicians and to consumers upon request or upon physician referral, in laboratories that clinical laboratory scientists may own or operate. Clinical laboratory scientists exercise prudence and judgment to ensure that such services are consistent with good practice and sound professional ethics.[3]

DIRECTORS OF FULL-SERVICE CLINICAL LABORATORIES

Non-physician clinical laboratory scientists, with the appropriate graduate education, direct full-service clinical laboratories. This function is firmly grounded in (a) the applicable country's law and (b) government guidelines governing clinical laboratories.[4]

Consultants for Clinical Laboratory Services

Clinical laboratory scientists may appropriately provide technical assistance to physicians, manufacturers, and consumers of clinical laboratory testing services, including: advising upon the design and service scope of clinical laboratories; advising physicians in the appropriate utilisation, selection and sequencing of clinical laboratory tests and, in collaboration with attending physicians, determining clinical correlations and interpretations of the quality and utility of specific laboratory results; advising manufacturers upon the design and development of clinical laboratory instruments, test kits and other components; and advising other users and consumers of clinical laboratory testing services upon appropriate use, maintenance, quality assurance and other procedural and informational requirements.

Providers of Disease-State Risk and Wellness Assessments

Clinical laboratory science is distinct from the practice of medicine, which renders diagnosis and provides treatment for human beings. While clinical laboratory scientists provide critical information, they do not diagnose or prescribe treatments. They are qualified by education and experience to perform screening tests to identify the presence or absence of factors known to be associated with risks for disease or impairment. Such services may include but are not limited to performing and reporting to consumers the results of tests to determine blood cholesterol levels and the presence or absence of metabolised substances of abuse. In all such cases, clinical laboratory scientists are bound by applicable laws and regulations, as well as by standards of good practice and sound professional ethics, in their relationships with consumers and with practitioners of medicine.

LEVELS OF PRACTICE

For each of the three functions of clinical laboratory science practices — scientific, managerial and educational — there are hierarchical levels of practice, based upon education and experience. Specific knowledge and experience are required for each level of practice within the three functions. As an individual gains experience and education, the individual is eligible, after demonstrating competence, to practice at that level. Certain knowledge and experience are common to all three functions; none is mutually exclusive of the others. Demands of the health care environment often require an individual to provide more than one function, thereby performing at different levels of practice.

The scientific function includes the production of test data, monitoring the accuracy, precision and utility of laboratory testing, the correlation and interpretation of test data, and the design, evaluation and implementation of new laboratory test methods.

The managerial function includes managing all aspects — technical, fiscal, workflow, and human resources — of laboratory operations.[5]

The educational function includes the establishment and management of educational programs for new and current clinical laboratory practitioners, other healthcare providers and consumers.[5]

QUALIFICATIONS FOR PRACTICE

Personnel standards should be prescribed for **ALL** personnel, including directors, supervisors, clinical laboratory scientists and other laboratory technical personnel, to ensure the accuracy and reliability of test performance.

- The individual qualified to perform clinical chemistry tests must demonstrate competency and performs simple tests requiring little to no independent judgment and interpretation.

- The individual qualified to perform complex tests must demonstrate competency as a Clinical Laboratory Technician and performs, under direct supervision, more technically demanding tests with some degree of independent judgment and interpretation.
- The individual qualified to perform highly complex tests must demonstrate competency as a Clinical Laboratory Scientist and performs more technically complex tests requiring considerable amounts of independent judgment and interpretation.
- The benchmark for the Clinical Laboratory Scientist is a baccalaureate degree as awarded by a regionally accredited college/university including or in addition to successful completion of a clinical laboratory scientist program
- The benchmark for the Clinical Laboratory Technician is an associate degree as awarded by a regionally accredited college/university including successful completion of a clinical laboratory science technician program

The knowledge economy, in which " knowledge work[s] on knowledge to create value," has become the wheel of economics.[2] Medical technology, and therefore the economic backbone of the health care system, has undergone a vast transformation, with information technology making it a high-tech industry. Global competitiveness has resulted in cost containment measures. The industry has become fragmented, fractured, and redundant, and it runs to excess capacity.[6] In such a pressurised atmosphere, one needs to understand that laboratory professionals are restricted to analyses, technical details, and organisational and managerial components of the profession as previously delineated. Now it is believed that laboratory professionals could also apply themselves to the creation, distribution and application of knowledge related to laboratory-based patient care.

Laboratory tests could be simple routine tests, with moderately complex tests followed by highly complex tests like genomic and proteomic analysis. Therefore, the laboratory professional has a responsibility to educate the primary care and secondary care physicians regarding these clinical laboratory investigations.

In particular, nanotechnologies are expanding the field of diagnostics with therapeutics and the development of personalised medicine. Nanotechnology is spreading in the field of innovating new markers, cancer diagnoses and microbiological investigations. The safety measures involving in vivo use is the core ethical concern.[7]

Therefore, there is a great need for formulating ethical guidelines and principles to govern modern clinical laboratory science starting from analytical to human resource development. It would be appropriate for ethicists, philosophers and clinicians to formulate a code of ethical guidelines to run these laboratory services that play a major role in health and disease.[8]

There is now a real need to consider clinical chemistry professionals like any other professionals in the healthcare system, such as physicians, dentists, pharmacists and nurses. Since many gain qualifications in the field of clinical laboratory practice, they need to be given a license like, for example, a pharmacist. That license must be given only to those who are qualified clinical chemistry laboratory professionals. Only those licensed clinical chemistry professionals can practice and open clinical laboratories individually or in private or public sector hospitals. Such a mandatory licensing system will help run the profession efficiently and guarantee employment opportunities to those who specialise in this field.

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NOSOCOMIAL RETROPERITONEAL SUPPURATIVE KIDNEY INFECTIONS: ANTIMICROBIAL SUSCEPTIBILITY

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NOZOKOMIJALNE RETROPERITONEALNE SUPURATIVNE BUBREŽNE INFEKCIJE: ANTIMIKROBNA OSETLJIVOST

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ABSTRACT

The microbiological pattern of nosocomial retroperitoneal suppurative kidney infections has not yet been studied, probably due to their very rare occurrence. Our aim was to identify pathogens involved in such infections and determine their antimicrobial susceptibility. This multicentre, retrospective case-control study involved data from urological clinics in Serbia. A variety of common clinical parameters were studied, with emphasis on the microbiological pattern of these infections. Urinary tract pathogens were identified, and the susceptibility to 9 antimicrobials was determined. Descriptive statistics and logistic regression were used for data analysis. In a total sample of 93 adult subjects with renal suppuration, we found 19 cases of nosocomial origin and 74 controls. The results of the final regression show that a history of malignancy and chronic renal failure significantly increased the risk of developing nosocomial retroperitoneal infection (odds ratio [OR] OR = 22.3, OR = 4.8, respectively). Overall, 67 types of bacteria were isolated in 15 cases and 36 controls. There were significant differences between cases and controls in isolated Pseudomonas aeruginosa (OR = 6.6), mixed pathogens (OR = 6.9), number of pathogens (OR = 2.1), and Gram-positive bacteria (OR = 6.3). Resistance rates for all agents except carbapenems and for all Gram-negative organisms were higher in isolates from cases than controls. There were significant differences in bacterial susceptibility to ceftriaxone, cefotaxime and ofloxacine in cases compared to controls. Our results represent an initial step in defining a high-risk group that merits intensive infection control efforts, and they can be used to prepare locally applicable recommendations for the optimal empirical therapy of suppurative kidney infection patients.

Key words: *bacterial resistance, empirical therapy, nosocomial retroperitoneal infection.*

SAŽETAK

Mikrobiološki uzorci nozokomijalnih retroperitonealnih gnojnih bubrežnih infekcija do sada nisu ispitivani verovatno usled njihove retke učestalosti. Otuda, naš cilj je bio da utvrdimo uzročne patogene i odredimo njihovu antimikrobnu osetljivost. U milticentričnoj, retrospektivnoj studiji slučaj-kontrola uključeni su podaci iz uroloških Srpskih klinika. Sakupljani su različiti uobičajeni klinički parametri, ali su mikrobiološki uzorči naročito ispitivani. Urinarni patogeni su identifikovani i određena je njihova osetljivost na 9 antimikrobnih lekova. U analizi podataka korišćene su metode deskriptivne statistike i logističke regresije. U ukupnom uzorku 93 odrasla bolesnika sa gnojnim renalnim infekcijama mi smo utvrdili 19 slučajeva nozokomijalnog porekla i 74 kontrola. Rezultati multiple regresije pokazali su da anamneza maligniteta i hronične renalne slabosti značajno povećavaju rizik pojave nozokomijalnih retroperitonealnih infekcija (unakrsni odnos [OR] OR = 22.3, OR = 4.8, respektivno). Ukupno, 67 bakterija je izolovano iz 15 slučajeva i 36 kontrolna bolesnika. Između grupe slučajeva i kontrola utvrđena je značajna razlika u izolaciji Pseudomoas aeruginosa-e (OR = 6.6), mešanih patogena (OR = 6.9), broja patogena (OR = 2.1), i Gram pozitivnih bakterija (OR = 6.3). Rezistencija prema svim lekovima i kod svih Gram-negativnih patogena bila je viša u izolatima iz slučajeva u npoređenju sa kontrolama, osim prema karbapenemima. Utvrđena je značajna razlika bakterijske osetljivosti prema ceftriaxonu, cefotaximu i ofloxacinu u slučajevima u poređenju sa kontrolama. Naši rezultati pretstavljaju inicijalni korak u definisanju visokorizične grupe bolesnika koji zahtevaju intenzivne napore u prevenciji infekcija i mogu se upotrebiti za lokalno primenljive preporuke optimalne empirijske terapije bolesnika sa gnojnim renalnim infekcijama.

Ključne reči: *bakterijska rezistencija, empirijska terapija, nozokomijalne retroperitonealne infekcije.*

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INTRODUCTION

Urinary tract infections (UTIs) are among the most common nosocomially acquired infections (1) and account for about 40% of these infections (2). The incidence of nosocomially acquired urinary tract infections (NAUTIs) in a large European population reached 3.55/1000 patient-days (3), burdening hospitals with significant extra costs (4).

NAUTIs are largely associated with urinary catheterisation or other urinary tract instrumentation. These infections typically affect patients who are immunocompromised because of age, underlying disease, or medical or surgical treatment. The antimicrobial susceptibility and treatment options for these infections differ significantly from those of infections that are community-acquired. The large majority of these infections have been considered relatively innocuous, as they are associated with little mortality or prolongation of hospital stay. On the other hand, one subgroup of NAUTIs, suppurative kidney infections that appear during hospitalisation, represent a different clinical entity as these more seriously affect patients and put them at increased risk of unfavourable outcomes. In the clinical situation, the results of culture are usually not known when treatment is started; since the initiation of antibiotic therapy cannot be delayed for long in these patients, it must therefore be started empirically.

So far, an extensive range of antibiotics has been suggested for these invasive and difficult-to-treat conditions; however, to our knowledge, the optimal therapy remains unknown. It is generally thought that empirical treatment regimens in nosocomial blood stream infections must include coverage for Pseudomonas sp (5). However, little is known about the spectrum and the susceptibility of pathogens that cause nosocomial suppurative kidney infections, and due to the rarity of these infections, no definitive guidelines for treatment based on prospective studies exist.

Given this background, our aim was to obtain baseline data from retroperitoneal suppurative kidney infection patients, to establish the pathogens involved, and to determine the susceptibility of the causative pathogens to different antimicrobial agents so that optimal empirical therapy can be initiated in such patients.

PATIENTS AND METHODS

Case definition, selection of control subjects and data collection

In this case-control study design, we retrospectively reviewed medical records obtained between 2000 and 2007 at three tertiary referral Serbian urology clinics (Institute of Urology and Nephrology Belgrade, Clinic of Urology and Nephrology Kragujevac and Clinic of Urology Nis). Nosocomial retroperitoneal infections or so-called nosocomial acquired other urinary tract infections (NAOUTIs) (for cases) were defined according to the Centers for Disease Control and Prevention (CDC) in the USA (6). A case of nosocomial retroperitoneal infection was defined as any patient with such an infection and known causative factor of nosocomial origin (permanent catheters, long-term ureteral stent, recently operated patients or other urological intervention). Control subjects were defined as those with retroperitoneal infections without a known causative factor related to hospital environment.

Collected data included demographic information (sex, age), laboratory findings (sedimentation rate, white blood cell count, haemoglobin and serum creatinine level), important comorbid conditions (diabetes mellitus, malignancy, urolithiasis/obstruction, chronic renal failure, general frailty due to systemic organic insufficiency and overall number of comorbid conditions). We also evaluated imaging findings including those of affected retroperitoneal structures. Suppurative pathological processes were classified into two groups, one representing suppuration confined within renal boundaries and including renal abscesses and pyonephroses only, and another representing suppuration beyond the renal boundary and including extension of pyonephrosis or intrarenal abscesses into perirenal tissue, or dominant perirenal collection.

Identification, isolate selection and susceptibility testing methods

Specimens were cultured and bacterial isolates identified using standard microbiological techniques (7). All isolates with bacterial counts of >103 cfu/mL were included in the study. In the case of mixed cultures, no more than two bacteria (those with the two highest counts) were identified. For analysis of subjects' cultures, isolates were divided into four groups: Enterobacteriaceae and non-Enterobacteriaceae from cases and the same species from controls.

Antimicrobial susceptibility was determined by the standard disc diffusion method recommended by the Clinical Laboratory Standards Institute (CLSI) (8). Intermediate categories of susceptibility or resistance were not used; any such isolates were recorded as resistant and referred to as 'non-susceptible' (9). Duplicates were excluded on the basis of species, individual and time (exclusion cut-off of 7 days) from the first isolate - isolation rank (8). In the case of mixed cultures, only the major pathogen was tested.

According to the recommendations of the CLSI Guidelines (8) (a minimum of ten strains are required for separate reporting, with a proposal to use a threshold of at least 25 strains), antimicrobial susceptibility results for Gram-negative isolates were divided into two groups: those from cases and those from controls. Results were also calculated for all (total) isolates. Due to the small number of Gram-positive isolates, susceptibility testing was not performed.

Gram-negative bacteria were tested against the following antimicrobial agents: trimethoprim and sulfamethoxazole (in combination), gentamicin, amikacin, ciprofloxacin, ofloxacin, ceftriaxone, cefotaxime, antipseudomonal cephalosporins and carbapenems (since the beginning of 2003).

Risk factors	Controls n=74 (79.6%)	Cases n=19 (20.4%)	OR (95% CI)	p value
Patient characteristics				
Onset of disease (days)	16, 50	7, 9	0.963 (0.928 – 0.999)	0.046*
Age (years)	57.7 ± 14.4	53.2 ± 9	0.975 (0.938 – 1.013)	0.190
Sex male/female	28/46	11/8	0.443 (0.159 – 1.234)	0.119
SE (mm/h)	100 ± 33.6	111.7 ± 24.6	1.012 (0.995 – 1.031)	0.175
WBC ($x10^9$/L)	12.4, 10	11.4, 10.9	0.98 (0.917 – 1.048)	0.561
Hgb (g/dL)	10.05 ± 1.84	9.67 ± 1.64	0.988 (0.959 – 1.017)	0.41
Creatinine (µmol/L)	120, 103	170, 547	1.002 (1.0 – 1.003)	0.049
Comorbidity				
Diabetes no/yes	57/17	16/3	0.629 (0.164 – 2.418)	0.500
Chronic renal failure no/yes	66/8	12/7	4.812 (1.470 – 15.76)	0.009*
urocalculosis/ob-struction no/yes	14/60	6/13	0.506 (0.164 – 1.563)	0.236
Malignancy no/yes	71/3	10/9	21.3 (4.92 – 92.16)	<0.001*
Frailty no/yes	64/10	17/2	0.753 (0.151 – 3.766)	0.730
Number of comorbid conditions	1, 1	2, 1	1.982 (1.075 – 3.656)	0.028*
Pathology 0/1**	29/45	9/10	0.716 (0.260 – 1.975)	0.519

* significant differences; ** see text for explanation; SE = erythrocyte sedimentation rate; WBC = white blood cell count; Hgb = haemoglobin level.

Table 1: Baseline patient characteristics (N=93).

Statistical analysis

We expressed continuous variables as the mean and standard deviation (SD) when normally distributed, or as the median and interquartile range (IQR) if their distribution was skewed, and discrete variables as percentages. We tested research hypotheses using Student's unpaired t-test or the Mann–Whitney U-test (for continuous variables) and the $\chi 2$ or Fisher exact test (for frequencies), all two-tailed. Univariate analysis was initially carried out to search for statistically significant variables associated with NAOUTIs. Multiple logistic regression models were used to measure the magnitude and significance of the association between NAOUTIs and particular characteristics. The strength of association between various factors and NAOUTIs was reported in term of an odds ratio (OR) with a 95% confidence interval (CI). The probability level for significance for all calculations was established at $p<0.05$.

RESULTS

Patients' characteristics

This study included 81 patients with 93 retroperitoneal infections (12 [12.9%] with recurrent infections [median, interquartal range 7, 19, range = 1–48 months]), of which 19 (20.4%) were of nosocomial origin (cases) and 74 (79.6%) were classified as controls. Patients' ages ranged from 21 to 80 years, with a mean of 53 years for cases and 58 years for controls. Males constituted 41.9% (39) of the study patients. Other significant patient characteristics (onset of disease, laboratory data (erythrocyte sedimentation rate, white blood cell count, haemoglobin levels, blood creatinine), predisposing medical conditions, diabetes mellitus, chronic renal failure, urolithiasis/obstruction, malignancy, general frailty due to systemic organic insufficiency and overall number of comorbid conditions) of the cases and controls are detailed in Table 1.

The types of procedures in the cases were as follows: 6 (31.6%) occurred after open surgery, of which 3 occurred after nephrectomies and 3 after cystectomies; 4 (21%) after insertion of long-term ureteral stents, 2 (10.5%) after endoscopic surgery, 2 (10.5%) after long-term transurethral urinary catheter, 2 (10.5%) after percutaneous nephrostomy or cyst aspiration, 2 (10.5%) after superinfection of long-term drainage catheters and 1 (5.3%) after renal arteriography and embolisation.

In the unadjusted analyses, there were no significant differences between cases and controls in age, sex, diabetes, urolithiasis/urinary tract obstruction, general frailty, sedimentation rate, white blood cell count, or haemoglobin levels. However, this analysis showed significant differences between cases and controls in chronic renal failure, history of malignancy, blood creatinine, and median number of comorbid conditions (OR = 4.812, 95% CI 1.470–15.76, p = 0.009; OR = 21.3, 95% CI 4.92–92.16, $p < 0.001$; OR = 1.002, 95% CI 1.0–1.003, p = 0.049; OR = 1.98 95% CI 1.07–3.66,

p = 0.028, respectively). There were no differences in the type of pathological processes (beyond renal boundaries) in cases compared to controls (52.6% [10 out of 19] versus 60.8% [45 out of 74], p = 0.519). The results of the final logistic regression model shown that history of malignancy and chronic renal failure significantly increased the risk of developing nosocomial retroperitoneal infection (OR = 22.248, 95% CI 4.744–104.926, p < 0.001; OR = 4.813, 95% CI 1.157–20.022, p = 0.031, respectively).

Microbiological data

Microbiological samples were not taken in 24 (25.5%) patients, and bacteria did not grow from the collected sample in 19 (20.4%) patients. Of the 49 urine cultures performed in 45 (48.4%) patients, 33 (67.3%) were sterile. Of the 62 pus cultures performed in 56 (60.2%) patients, 14 (22.6%) were sterile. Overall, we obtained microbiological data from 51 (54.8%) patients, 4 (7.8%) of whom underwent urine culture only. In 51 patients with positive cultures, 67 species of bacteria were isolated. The most common pathogen was Escherichia coli (20.4% of all patients), followed by Proteus mirabilis (15%) and Pseudomonas aeruginosa (13.9%). The distribution of bacteria and bacterial groups isolated from the subjects' cultures is shown in Fig. 1. Overall, 22 bacteria were isolated in 15 (78.9%) cases and 45 out of 36 (48.6%) ones with community-acquired collections.

There were significant differences in the frequency of isolated P. aeruginosa (OR = 6.611, 95% CI 1.892–23.104, p = 0.003), or non-Enterobacteriaceae (OR = 5.583, 95% CI 1.657–8.808, p = 0.006), Gram-positive bacteria (OR = 6.310, 95% CI 1.278–31.168, p = 0.024), mixed pathogens (OR = 6.961, 95% CI 2.101–23.068, p = 0.002) and number of pathogens (OR = 2.121, 95% CI 1.155–3.895, p = 0.015) between cases and controls. However, only the distribution of mixed pathogens (OR = 4.728, 95% CI 1.296–17.251, p = 0.019) was statistically significant in the final logistic model.

Antibiotic susceptibility testing of Gram-negative bacilli

Antimicrobial susceptibility, according to previously defined criteria, was determined for Gram-negative bacteria in 15 isolates from cases and 36 isolates from controls obtained from samples from 51 (54.8%) of the patients. Resistance rates for all agents and all Gram-negative organisms were higher in isolates from cases than in isolates from controls, except against carbapenems (100% susceptibility) (Table 2). There were significant differences in bacterial susceptibility to ceftriaxone, cefotaxime and ofloxacine (OR = 2.035, 95% CI 1.045–3.965, p = 0.037; OR = 5.020, 95% CI 1.575–15.995, p = 0.006; OR = 4.896, 95% CI 1.638–14.638, p = 0.004, respectively) in cases compared to controls.

DISCUSSION

Our study suggests that malignancy, chronic renal failure and short-term onset of disease significantly increase the risk for nosocomial acquired retroperitoneal infections. There are few reports in the literature defining the conditions that put patients suffering from kidney disease at risk for developing such infections. Investigators studying a wider spectrum of nosocomially acquired infections have also found that cancer patients are particularly prone to suppurative conditions (10). Appropriately focused prevention in these high-risk patients would ideally enhance the safety of hospitalised patients (11). However, prospective data are needed to assess the absolute risk of NAOUTIs in these patients because, given the relatively small number in our study, the estimate of the magnitude of the effect must be viewed with caution, although the results suggest a strong effect. Most of our cases presented with onset of disease in one week, which is similar to another study in which abscess appeared 10 ± 6 days after surgery (12).

Antimicrobial therapy, along with drainage of infected fluid accumulation, is recognised as the cornerstone of treatment for acquired infections (13). Many previous studies emphasised the importance of providing appropriate antimicrobial therapy to critically ill patients as early as possible and demonstrated that inadequate antibiotic treatment of hospital infections represents a strong independent factor related to increased hospital mortality (14). In the best-case scenario, effective therapy requires that the antibiotic agent be directed to the pathogens that are present, requiring that they be identified and their susceptibility patterns determined. However, in the clinical situation, the results of culture are usually not known when treatment is started; since the initiation of antibiotic therapy cannot be delayed for long, it must therefore be started empirically. Exact evidence about the microbiology of retroperitoneal suppurative infections is lacking, most likely due to their very low incidence; this places studies of

Table 2. Antimicrobial susceptibility rates (%) of uropathogens (N=51).

Antimicrobial agent	SXT	GEN	AMK	CIP	OFX	CRO	CTX	APC	CAP
Isolates tested	98	94.1	100	43.1	78.4	98	60.8	25.5	54.9
Overall susceptibility	26	51	84.3	27.3	47.5	70.6	61.3	84.6	100
Cases (n=15)	14.3	35.7	73.3	12.5	7.7*	50*	12.5*	66.7	100
Controls (n=36)	30.6	61.8	88.9	35.7	66.7	80.6	78.3	90	100

* significant differences; SXT = trimethoprim/sulfamethoxazole; GEN = gentamicin; AMK = amikacin; CIP = ciprofloxacin; OFX = ofloxacin; CRO = ceftriaxone; CTX = cefotaxime; APC = antipseudomonal cephalosporins; CAP = carbapenems.

their epidemiology at risk of underpowered study design. In order to increase sample size, in the present study we grouped bacterial species together, extended the period of observation, pooled intermediate isolates with resistant ones, and finally excluded duplicate strains (15) according to previous recommendations (8). We therefore believe that our results provide reasonable epidemiological indicators, useful for both public health services and clinicians.

Comparison of our findings on the microorganisms most commonly isolated from nosocomial infections with previously published results shows a broadly similar picture (4, 16). In one study, the most common pathogens found in 114 abscesses after 32,284 operations were Escherichia coli, enterococci, and Bacteroides organisms (12). In retroperitoneal infections due to community-acquired methicillin-resistant Staphylococcus aureus, perinephric tissue was the most affected site (17). A recent study by Lee et al. (18) reported clinical and microbial differences between cases with renal and perirenal abscesses. We, however, did not find differences in type of pathological process with respect to specific causative factors.

Numerous studies have shown that uropathogens isolated from nosocomial UTIs tend to have a higher antibiotic resistance than those isolated from community-acquired UTIs (19-21); this was confirmed in our study. Our findings on effective antimicrobial therapy are also in concordance with recommendations in the treatment community for nosocomially acquired complicated urinary tract infections or urosepsis (22). Two main reasons may explain this observation: a higher proportion of naturally resistant species among bacteria of nosocomial origin (e.g., P. aeruginosa) as well as a higher proportion, within a given species, of isolates with acquired resistance traits that cause nosocomial infections (19). Based on this reasoning, highly active agents with low potential for inducing resistance, such as amikacin and antipseudomonal beta-lactams, should be the most optimal choice for treatment (9). In other UTIs, less-powerful drugs such as broad- spectrum cephalosporins, fluoroquinolones, aminopenicillins, gentamicin, and co-trimoxazole constitute a more rational alternative (23), particularly since surveillance data showed that resistance rates for these drugs did not reach predefined, critical levels (24). The establishment of critical levels for particular bacterium–antibiotic combinations depends mainly on the severity of the infection and on the availability of alternative therapies. Furthermore, if surveillance detects resistance in a dangerous organism, and no or few alternative drugs are capable of controlling it, even a very low resistance rate should be considered high risk (9).

The results of our study should be interpreted carefully, taking into account inherent difficulties arising from issues regarding temporal trends (25), thresholds for isolate numbers, random fluctuation, differences of resistance breakpoints between observed levels and national standards, semiquantitative interpretation of sensitivity testing (9) and regional (20) or institutional differences (26). In spite of these concerns, a major advantage of the data presented here is that they allow an up-to-date surveillance system to be created simply by regularly downloading data on a wide range of organisms and specimen types; for this reason, we believe that our study has important patient safety implications.

In conclusion, the data presented in this study indicate that antibiotics commonly used for the treatment of nosocomially acquired infection are less than optimally effective. Our results represent an initial step in defining a high-risk group that merits further regular monitoring; such monitoring can be used to obtain reliable information about the resistance patterns of urinary pathogens that can then be used to prepare locally applicable recommendations for the optimal empirical therapy of patients with suppurative kidney infections.

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PREGNANCY-ASSOCIATED PLASMA PROTEIN (PAPP-A) AS A PROGNOSTIC INDICATOR IN ACUTE CORONARY SYNDROMES

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PREGNANCY ASSOCIATED PLASMA PROTEIN (PAPP-A) U PROCENI RIZIKA KOD PACIJENATA SA AKUTNIM KORONARNIM SINDROMOM

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ABSTRACT

Despite diagnostic and therapeutic advances for acute coronary syndromes (ACS), the rate of event recurrence is still relatively high, and short- and long-term prediction of risk is necessary, although extremely challenging, to provide optimal treatment to patients. New markers of coronary artery disease progression have been identified in recent years, among which circulating levels of pregnancy-associated plasma protein-A (PAPP-A) offer an interesting profile. This protein is expressed in eroded and ruptured atheromatous plaques, and circulating levels are elevated in ACS. Available data indicate the use of PAPP-A as a prognostic marker in patients with ACS in addition to other prognostic factors, including C-reactive protein (CRP) and troponin levels. Simultaneous determination of biomarkers with distinct pathophysiological profiles appears to remarkably improve risk stratification in patients with ACS.

Keywords: *Pregnancy-associated plasma protein A, acute coronary syndromes*

SAŽETAK

Uprkos savremenim dijagnostičkim i terapijskim metodama, stopa neželjenih događaja je i dalje visoka kod pacijenata sa akutnim koronarnim sindromom, stoga je nepohodna bolja procena kardiovaskularnog rizika. Poslednjih godina otkriveni su novi biomarkeri za procenu progresije koronarne bolesti, među kojima je i pregnancy-associated plasma protein-A (PAPP-A). Pregnancy-associated plasma protein-A (PAPP-A) je izolovan u ruptuiranim aterosklerotskim plakovima i nalazi se u povišenoj koncentraciji u krvi pacijenata sa akutnim koronarnim sindromom. Rezultati dosadašnjih studija pokazali su da je PAPP-A koristan marker u proceni kardiovaskularnog rizika kod pacijenata sa akutnim koronarnim sindromom zajedno sa C-reaktivnim proteinom i troponinima.

Uporedno određivanje različitih biomarkera značajno poboljšavaju stratifikaciju rizika kod pacijenata sa akutnim koronarnim sindromom.

Ključne reči: *Pregnancy-associated plasma protein A, akutni koronarni sindrom*

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INTRODUCTION

Coronary atherothrombotic disease (CAD) often results in serious adverse cardiovascular (CV) events, despite aggressive treatment. These future events are usually due to thrombus formation at the site of a ruptured or eroded atherosclerotic plaque, and they are characterized clinically as acute coronary syndrome (ACS) (1). There is solid evidence that has established CV risk factors, including dyslipidemia, smoking, hypertension and diabetes mellitus, which can be incorporated into algorithms for risk assessment in the general population (2). It is well known, however, that these characteristics do not fully explain CV risk (3). Measurements of cardiac biomarkers might, therefore, independently predict risk beyond conventionally used stratification tools and may also give a reliable indication of CV risk in patients with ACS (4,5).

The elevation of biomarkers indicates the onset of several harmful mechanisms that place the individual patient in a high-risk category.

THE PREGNANCY-ASSOCIATED PLASMA PROTEIN A (PAPP-A): A NOVEL AND PROMISING MARKER OF CORONARY HEART DISEASE

The pregnancy-associated plasma protein A (PAPP-A) is a zinc-binding enzyme belonging to the metalloproteinase superfamily, with a high molecular weight (6,7). It was first identified as a circulating protein in the serum of women in advanced stages of gestation (8). Measurement of PAPP-A is useful for screening the foetus for Down syndrome within the first 3 months of pregnancy, as decreased circulating concentrations of this protein are associated with abnormal placental function (8). In addition to placental tissue, PAPP-A is present in a wide variety of reproductive tissues and organs, such as the testicles and endometrium; it is also present in non-reproductive tissues, such as the kidney and colon, but at much lower concentrations than those found during gestation (9). Pregnancy associated plasma protein A is also secreted by osteoblasts, cells of the granular layer of the ovary and vascular smooth muscle cells (10). The circulating form of the protein comprises a heterotetrameric complex formed of two subunits that are 200 kDa and 250 kDa and bound by covalent bonds to two molecules that are 50 kDa and 90 kDa that belong to the proform of eosinophil major basic protein, an endogenous inhibitor of the proteolytic activity of PAPP-A (11). A highly sensitive immunoassay is required to detect PAPP-A protein in normal clinical situations because the concentrations of PAPP-A are 100 times less in the normal population than in gestating women (9). The protein is a specific protease whose substrate is insulin growth factor (IGF), a factor similar to insulin, and one of the IGF binding proteins, IGFBP-4. When IGF is released from its binding to this protein, PAPP-A appears as a growth modulator in local proliferative responses to IGF, such that it influences the role played by IGF in the pathogenesis of atherosclerosis (12). These actions would give it an important role in the progression of atherosclerosis and the development of restenosis after coronary interventions.

Methods

We searched for published and unpublished studies reported from 2001 to 2009 in PubMed (http://www.ncbi.nlm.nih.gov). The electronic search strategy was constructed using the keywords "pregnancy-associated plasma protein A" combined with "coronary artery disease" or "acute coronary syndromes" or "myocardial infarction" or "unstable angina pectoris" in text words or medical subject headings.

We restricted our search to studies of humans and written in English.

We assessed all observational studies published from 2001, when PAPP-A was first considered as a biological marker of unstable atherosclerotic plaques. We included all studies that assessed the association between PAPP-A and acute coronary syndrome (ACS). Studies in which observed patients had stable angina pectoris were excluded.

Results

We found and reviewed 29 references identified through PubMed, 17 of which were excluded after analysing the abstract provided because they did not meet the inclusion criteria.

Five studies assessed the levels of PAPP-A in 306 patients (in total) admitted to the hospital with ACS.

The prognostic role of PAPP-A was investigated in five studies. Cumulatively, these studies included almost 1500 patients. The time of follow-up was from 1 to 12 months. The primary end-point of all studies was cardiovascular death, non-fatal myocardial infarction or revascularisation.

We also included two studies in which the authors attempted to determine the PAPP-A levels after PCI and thrombolytic therapy in ACS in almost 200 patients.

PREGNANCY-ASSOCIATED PLASMA PROTEIN A IN ACUTE CORONARY SYNDROMES

Pregnancy-associated plasma protein A was first considered as a biological marker of unstable atherosclerotic plaques in 2001 after a study by Bayes-Genis et al., who examined the level of expression of PAPP-A in eight culprit unstable coronary plaques and four stable plaques from eight patients who had died suddenly of cardiac causes (13). These authors found that PAPP-A was abundantly expressed in plaque cells and the extracellular matrix of ruptured and eroded unstable plaques, but not in stable plaques (13). Circulating PAPP-A levels were significantly higher in patients with unstable angina or acute myocardial infarction (AMI) than in patients with stable angina and controls ($P < 0.001$). A PAPP-A threshold value of 10 mLU

per litre identified patients who had ACS with a sensitivity of 89.2% and a specificity of 81.3%. PAPP-A levels correlated with free IGF-I and CRP but not with markers of myocardial damage (creatine kinase MB isoenzyme [CK-MB] and troponin I [TnI]). Khosravi et al. (9) also investigated associations of PAPP-A with myocardial damage in serum samples classified based on serum creatine kinaze CK-MB or cardiac troponin-T levels. They found a strong correlation between PAPP-A and Troponin-T ($r = 0.59$, $p < 0.001$) in a subset of troponin-T-positive samples. Opposite results of these studies regarding the correlation of PAPP-A with markers of myocardial damage might be due to the fact that PAPP-A has also been associated with other cardiac markers that could be influenced by their relative release dynamics (i.e., timing and duration). Contrary to the findings of these studies, a study by Domínguez-Rodríguez et al. (14) found no differences between the PAPP-A concentrations in 80 patients with ST-elevation ACS compared to control subjects (26). The authors concluded that PAPP-A is not a valid early marker of AMI. This same study also did not find any correlation between PAPP-A and markers of myocardial necrosis; samples were taken at 6.3 ± 2.8 hours (mean ± SD) after the onset of symptoms.

In another study with 59 patients presenting with chest pain to the emergency department (ED), elevated serum PAPP-A levels were found to be predictive of a diagnosis of ACS in intermediate- to high-risk patients with chest pain and no definite evidence of ACS (15). Thus, serum PAPP-A may be valuable as an adjunct, minimally invasive marker to improve risk stratification in patients presenting with chest pain.

Schoos et al. assessed 40 patients grouped according to type of ACS (16). In this study, PAPP-A concentrations were measured in serially collected samples. All patients with elevated PAPP-A levels reached the upper reference level within 24 h. There was a significant difference in median peak levels between STEMI (23.2 mIU/L) and low-risk ACS patients (6.35 mIU/L) ($p = 0.004$) and between high-risk (median = 15.3 mIU/L) and low-risk ACS patients ($p = 0.01$). Among high-risk ACS patients, NSTEMI patients had significantly higher peak levels than unstable angina patients ($p = 0.003$).

PROGNOSTIC VALUE OF PAPP-A IN ACUTE CORONARY SYNDROMES

Several studies have demonstrated that PAPP-A may have prognostic value in patients with ACS. Some reports have also examined the risk stratification of patients by PAPP-A alone or in combination with cardiac troponins.

The role of PAPP-A as a prognostic indicator in ACS patients has been assessed in several studies. Laterza et al. (17) tried to determine ability of circulating concentrations of PAPP-A to predict adverse events in patients presenting to the ED with symptoms of ACS (n = 346 patients, of whom 33 suffered adverse events) (27). On analysis of the receiver operating characteristic (ROC) curves, cardiac troponin T (TnT) was found to be a better predictor of events after 30 days than PAPP-A. For a cut-off point of 0.22 mU/L, PAPP-A had a significantly worse specificity than cardiac TnT. Thus, according to this study, PAPP-A was a modest predictor of adverse coronary events 30 days after the index event (17).

In another study, Lund et al. (18) assessed 200 consecutive patients with suspected ACS and undetectable concentrations of TnT for up to 24 hours from admission. Patients with PAPP-A concentrations greater than 2.9 mU/L were at a significantly higher risk of cardiovascular death, a first episode of nonfatal AMI, or need for revascularization after 6 months of follow-up. At a cut-off level of 2.9 mIU/L, elevated PAPP-A was an independent predictor of adverse outcome (adjusted risk ratio [RR], 4.6; 95% confidence interval [95% CI], 1.8 to 11.8; $p = 0.002$). Another independent predictor was admission CRP >2.0 mg/L (RR, 2.6; $p = 0.03$).

Heeschen et al. also showed that determination of PAPP-A provides additional prognostic information in patients with ACS (19). Their study included 547 patients with ACS who underwent coronary angiography before randomization and a heterogeneous group of 626 consecutive patients with acute chest pain lasting less than 12 hours before admission. Blood samples were collected at the time of arrival in the ED (5.1 ± 3.4 h after onset of symptoms and before initiation of treatment), and a second blood sample was drawn 4 h later. PAPP-A and markers of myocardial necrosis (troponin T [TnT]), ischemia (vascular endothelial growth factor [VEGF]), inflammation (high-sensitivity C-reactive protein [hsCRP]), anti-inflammatory activity (interleukin [IL]-10) and platelet activation (soluble CD40 ligand [sCD40L]) were determined. In patients with ACS, elevated PAPP-A levels (above 12.6 mU/L) had a higher incidence of death or nonfatal myocardial infarction, with an odds ratio of 2.74 (95% CI, 1.44 to 5.22; $p = 0.002$) after 72 hours, 2.84 (95% CI, 1.55 to 5.22; $p = 0.001$) after 30 days and 2.44 (95% CI, 1.43 to 4.15; $p = 0.001$) after 6 months. When the analysis was restricted to TnT-negative patients, PAPP-A still identified a subgroup of high-risk patients (odds ratio [OR] 2.72 [95% CI, 1.25 to 5.89]; $p = 0.009$). Prospective validation in patients with chest pain confirmed that PAPP-A levels reliably identified high-risk patients (adjusted OR 2.32 [95% CI 1.32 to 4.26]; $p = 0.008$). An interaction between PAPP-A and interleukin (IL) 10 was shown such that the predictive value of the composite endpoint of death and nonfatal AMI was limited to patients with circulating IL10 concentrations below 3.5 ng/mL. The authors, therefore, concluded that the balance between proinflammatory and anti-inflammatory cytokines determined the course of the disease in these patients, who, in turn, had a higher rate of revascularization procedures. In this study, PAPP-A was also weakly correlated with other biological makers, such as hs-CRP and CD40L, although no correlation was found with TnT (19).

In a small cohort of patients with ST-segment elevation acute MI (n = 62), Lund et al. (20) noticed an early peak of circulating PAPP-A during the 12 h from symptom onset, followed by rapid normalization. Admission PAPP-A levels did not correlate with admission C-reactive protein or cardiac troponin I. The variability of PAPP-A kinetics at 48 h reflects the success of reperfusion. The authors also found that PAPP-A >10mIU/L was a significant predictor of 12-month risk of cardiovascular death or nonfatal MI.

Contrary to the findings of these studies, a recent study by Brugger-Andersen et al. in a patient population consisting of 298 subjects hospitalized with an MI found that a multi-marker approach with NT-proBNP, hsCRP, MMP-9, PAPP-A, MPO, sCD40L and FM rendered no additional prognostic information beyond conventionally used stratification tools in the acute phase (21).

THE EFFECT OF REPERFUSION THERAPY ON PAPP-A LEVELS IN ACUTE MYOCARDIAL INFARCTION

Brugger-Andersen et al. attempted to determine the PAPP-A levels after PCI and thrombolytic therapy with tenecteplase in a group of 38 patients admitted for STEMI (22). They found that the plasma concentrations of PAPP-A increased by a factor of six to eight times ($p < 0.001$) following both reperfusion therapies. Plasma concentrations of PAPP-A increased to a significantly higher level after PCI compared to thrombolytic treatment ($p = 0.002$). This would indicate a greater impact of PCI on the target coronary lesion due to a direct mechanical trauma, resulting in the local release of metalloproteinases into the extracellular space and henceforth systemically, whereas the increase in PAPP-A following thrombolytic therapy is likely derived from both target and systemic plaque vulnerability.

Terkelsen et al. found that PAPP-A was markedly elevated in the earliest hours after the onset of symptoms in patients with STEMI treated with heparin and primary percutaneous coronary intervention (23).

PREGNANCY-ASSOCIATED PLASMA PROTEIN-A AND ACUTE CORONARY SYNDROMES: CAUSE OR CONSEQUENCE?

There are controversial opinions regarding the role of PAPP-A in inflammatory reactions that lead to plaque rupture and clinical instability. Several lines of evidence indicate that PAPP-A is induced in response to and within damaged tissues as a promoter of repair, in virtue of its IGF-1-dependent actions on vasculogenesis, vasodilation, cell preconditioning, cell survival and insulin-sensitivity (24,25). Even mild damage, such as brief ischemia, would activate this pathway (12), thus explaining the higher sensitivity of PAPP-A compared to cardiac troponins as predictors of outcome. In response to necrosis, the broad-ranging fluctuations of PAPP-A justify its correlation with cardiac enzymes (18) and inflammatory markers. The remission of rheumatoid arthritis and other inflammatory states during pregnancy (the prototype of increased PAPP-A) denotes PAPP-A as a suppressor, rather than mediator, of inflammation and tissue damage (26).

In contrast, PAPP-A may have a more deleterious role by breaking down the extracellular matrix via its metalloproteinase character.

IGF-1 binds to the type I IGF receptor, which is present on many cell types found in the plaque (12). The outcome of IGF action on different cells, however, relates to other molecules and a complex microenvironment.

In macrophages, IGF promotes excess low-density lipoprotein cholesterol uptake, release of pro-inflammatory cytokines and chemotaxis. This inflammatory environment digests the fibrous cap, leaving the plaque vulnerable to rupture (12). PAPP-A cleaves IGF binding protein 4 and 5 in vitro (27) and may function similarly in vivo to enhance local IGF bioavailability. Recently, it has been demonstrated that PAPP-A expression is significantly enhanced by inflammatory cytokines, such as tumour necrosis factor- in adult human fibroblasts (28). If the same is found to be true in atherosclerotic plaques, increased PAPP-A will further increase levels of local bioactive IGF, thereby causing the plaque to proceed to disruption unless the chain of reactions is interrupted.

IGF-1 has a chemotaxtic action on vascular endothelial cells and induces endothelial tube-forming activity in vitro (12). The ultimate outcome, however, may be different because of the interactions between various bioactive molecules and cells within the atherosclerotic lesion. A recent study has shown that a long-term low dose of IGF-1 significantly enhances tumour necrosis factor- –induced adhesion molecule expression in endothelial cells, suggesting that IGF-1 is an enhancing factor for cytokine-induced endothelial cell inflammation (29).

In vitro IGF-1 plays an important role in migration, cell cycle progression and survival of vascular smooth muscle cells (12). However, there are studies showing that human plaque-derived vascular smooth muscle cells are not responsive to the protective effects of even high levels of IGF-1 in vivo because of reduced IGF-1 receptor expression and increased insulin-like growth factor binding protein synthesis, which can be caused by oxidized low-density lipoprotein, one of the important players in plaque inflammation (30).

Clearly, further studies are needed to prove the exact role of PAPP-A in atherosclerosis and its complications.

CONCLUSION

PAPP-A is a very promising novel biochemical marker for the prediction of first or recurrent coronary events either alone or as a complement to other markers. However, the findings are still preliminary and require further evidence to fully determine the true role of this marker and its application in clinical practice.

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HEART RATE-LOAD RELATIONSHIP UNDER DIFFERENT INCREMENTAL EXERCISE TEST PROTOCOLS

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ODNOS SRČANE FREKVENCIJE I OPTEREĆENJA U TOKU PRIMENE RAZLIČITIH PROTOKOLA INKREMENTALNOG TESTA OPTERĆENJA

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ABSTRACT

In this study, eight well-trained male subjects performed four laboratory treadmill protocols of increasing load. Heart rate was recorded continuously at 5 second intervals using a Polar heart watch (POLAR 610i) during each incremental exercise protocol. Protocol 1 was performed as follows: 10-minute warm up at 50% HR reserve starting at an initial speed of 8 km h^{-1}; running speed was increased by 1 km h^{-1} at each stage. Protocol 2 was performed as follows: 10-minute warm up at 50% HR reserve starting at an initial speed of 8 km h^{-1}; running speed was increased by 0.5 km h^{-1} at each stage. Protocol 3 was performed as follows: 10-minute warm up at 50% HR reserve starting at an initial speed of 10 km h^{-1}; running speed was increased by 0.5 km h^{-1} at each stage. Protocol 4 was performed as follows: 3-minute warm up at track speed of 3 km h^{-1}; starting at an initial speed of 3 km h^{-1}; running speed was increased by 0.5 km h^{-1} at each stage. The stage duration was kept constant at 1 minute in all protocols. The protocols lasted for as long as the subject could continue.

Depending on the applied protocol, the HR-L curve can be described by linear, polynomial (S-shaped), exponential or sigmoidal mathematical expressions. Our results indicate that the shape of the HR-L curve during incremental testing depends on the exercise protocol (change in initial speed and increment of running speed increase with a constant stage duration).

Keywords: *heart rate-load relationship, incremental exercise test*

SAŽETAK

U ovom radu primenili smo protokole za povećanje opterećenja kod 8 muških ispitanika koji su bili u dobroj kondiciji. Frekvencija srca se beležila neprekidno na svih 5 sekundi meračem POLAR HEART (POLAR610i) tokom 4 različita protokola povećanja opterećenja. Protokol 1 je izveden na sledeći način: 10 minuta zagrevanja sa 50 % rezerve frekvencije srca; početna brzina je bila 8 km/h -1; brzina trčanja je povećavana zap o 1 km-1 u svakoj fazi. Protokol 2 je izveden na sledeći način: 10 minuta zagrevanja sa 50% rezerve frekvencije srca; početna brzina je bila 8 km/h -1; brzina trčanja je povećana za po 0,5 km-1 u svakoj fazi. Protokol 3 je izveden na sledeći način: 10 minuta zagrevanja sa 50% rezerve frekvencije srca; početna brzina je bila 10 km/h; brzina trčanja je povećana za po 0,5 km-1 u svakoj fazi. Protokol 4 je izveden na sledeći način: 3-minutno zagrevanje brzinom od 3 km/h -1 brzina trčanja je bila povećavana zap o 0, 5 km-1 u svakoj fazi. Trajanje faze je održavano konstantno (jedan minut) u svakom protokolu. Protokoli su trajali onoliko koliko su ispitanici bili u stanju da izdrže.

U zavisnosti od primenjenog protokola, kriva u funkciji opterećenja frekvencije srca (HR-L) može se opisati linearnim, polinomalnim eksponencijalnim I sigmoidnim matematičkim izrazom. Naši rezultati pokazuju da oblik ove krive tokom testa postepenog povećanja opterećenja zavisi od primenjenog protokola vežbanja (promene brzine I povećanja brzine, uz nepromenjeno trajanje svake faze).

Ključne reči: *opterećenost frekvencije srca, test pojačanog vežbanja.*

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INTRODUCTION

It is well known that heart rate (HR) progressively increases during incremental load (L) increase. The relationship between HR and L is usually presented as a HR-L curve. However, the shape of HR-L curve during incremental exercise tests remains controversial. Brooke (1, 2) observed a nonlinear coupling of HR response to incremental workloads and suggested that the HR-L curve is sigmoidal (S-shaped). Many other authors (3, 4, 5) have confirmed those findings.

Conconi and co-workers (3) reported specific relationship between heart rate (HR) and increasing load during incremental exercise tests, pointing out the fact that a linear increase in heart rate is interrupted at the point near maximal exercise intensity. This point has been marked as the "heart rate deflection point", or HRDP. According to these authors, the HRDP occurs almost at the same time that blood lactate levels reach the anaerobic threshold. They concluded that if the work intensity above the AT increases more rapidly than HR, the deflection of HR could be used to assess AT. This specific relationship between heart rate (HR) and increased load during incremental exercise tests is the cornerstone of Conconi's test for non-invasive determination of AT.

Although the Conconi method is widely used, many authors have also reported a linear HR-L relationship during incremental maximal exercise tests, or that HR reaches a plateau only in a certain percentage of the subjects tested (6, 7).

It is obvious that questions remain about the shape of the HR-L curve. While Grazzi confirms the linearity of the HR-L curve (8), some authors define the HR-L curve as S-shaped, analyzing it using the triphasic behaviour of the lactate performance curve as the golden standard (9, 4). In addition, some authors propose the HR-L curve to be exponential (10).

It seems that the shape of HR-L curve can vary depending on numerous (still not clearly defined) factors, including the exercise protocol used. Therefore, we included an analysis of the influence of different exercise protocols on the shape of HR-L curve in this study.

Practical endurance performance has been evaluated with various tests that include not only heart rate, but also VO2, ventilator thresholds, EDV, ESV and other parameters. The purpose of this study was not to evaluate any of the aforementioned tests, but rather to analyze HR-L as a basic criterion for further incremental exercise testing.

PATIENTS AND METHODS

Subjects. Eight well-trained male subjects (age: 22.43 ± 4.04 years; weight: 72.87 ± 5.07 kg; height: 179. 26 ± 5.12 cm) volunteered to participate in the study. Medical observations (ECG, heart rate, arterial pressure, work activities, smoking habits, etc.) were made before testing, during the test period and 24 hours after the testing. The subjects were instructed not to perform any hard physical activity within 48 hours before the test. The clothing, shoes and equipment used, as well as the environmental conditions (room temperature at 21.3 ± 1.4°C, humidity at 42.4 ± 7.5%), were consistent for all the subjects.

The subjects received an explanation of the aims of the study, as well as detailed procedures, and they were given an opportunity to ask about anything that was unclear. All the procedures were performed according to the ethical standards of the local Ethics Committee and the Helsinki Declaration.

In order to evaluate the influence of different exercise protocols on the shape of the HR-L curve, we performed the following protocols for increasing load (L) on a laboratory treadmill (RX-17, RELAX, Serbia):

Protocol 1:
- 10 minute warm up at 50% HR reserve
- Initial speed of 8 km h^{-1}
- Running speed was increased by 1 km h^{-1} at each stage

Protocol 2:
- 10 minute warm up at 50% HR reserve
- Initial speed of 8 km h^{-1}
- Running speed was increased by 0.5 km h^{-1} at each stage

Protocol 3:
- 10 minute warm up at 50% HR reserve
- Initial speed of 10 km h^{-1}
- Running speed was increased by 0.5 km h^{-1} at each stage.

Protocol 4 –
- 3 minute warm up at 3 km h^{-1}
- Initial speed of 3 km h^{-1}
- Running speed was increased by 0.5 km h^{-1} at each stage.

In all protocols, the stage duration was kept constant at 1 minute. The protocols lasted for as long as the subject could continue.

Some of those protocols are not commonly used in literature (Protocol 1 and 2), but (according to our preliminary testing) they affect the shape of HR-L curve substantially (see below).

Heart rate (HR) determination.

HR was recorded continuously at 5 second intervals using a Polar heart watch (POLAR 610i). The last HR values for each stage were used for further analyses.

Data analysis. In order to estimate the dependence of heart rate on the load (HR-L curve), several mathematical formulas were tried. The mathematical expression that best fit the experimental data (i.e., with high correlation) depended on the protocol applied.

A linear equation (Eq. 1) fits the experimental data for the Protocol 1 (Fig. 1) with the highest correlation (R^2>0.99) :

$HR=aL+b$

where L is applied load; HR is heart rate; and a, b are parameters that define the shape of the curve.

A polynomial equation (Eq. 2) fits the experimental data for the Protocol 2 (Fig. 2) with the highest correlation (R^2>0.99):

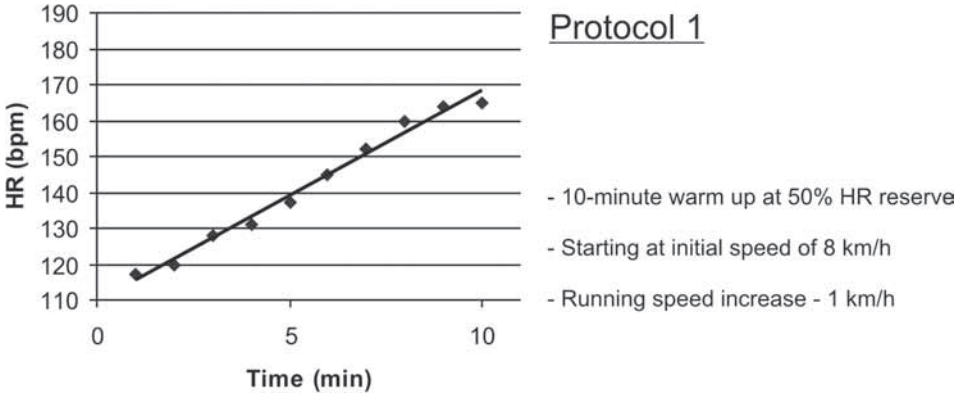

Figure 1. Original data obtained for one subject performing Protocol 1, fitted with the appropriate mathematical expression. Stage duration was constant (1 minute).

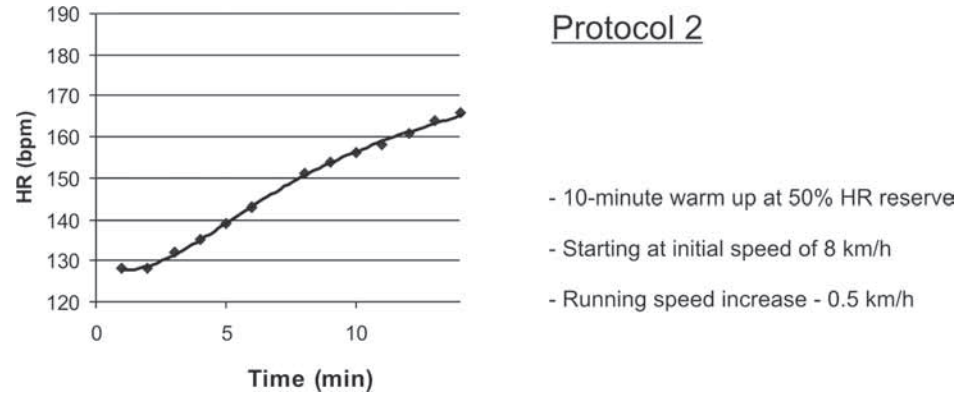

Figure 2. Original data obtained for one subject performing Protocol 2, fitted with the appropriatemathematical expression. Stage duration was constant (1 minute).

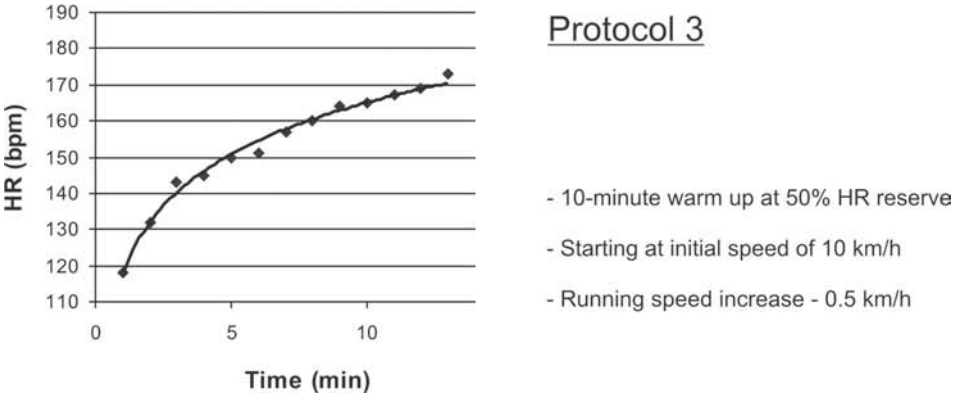

Figure 3. Original data obtained for one subject performing Protocol 3, fitted with the appropriate mathematical expression. Stage duration was constant (1 minute).

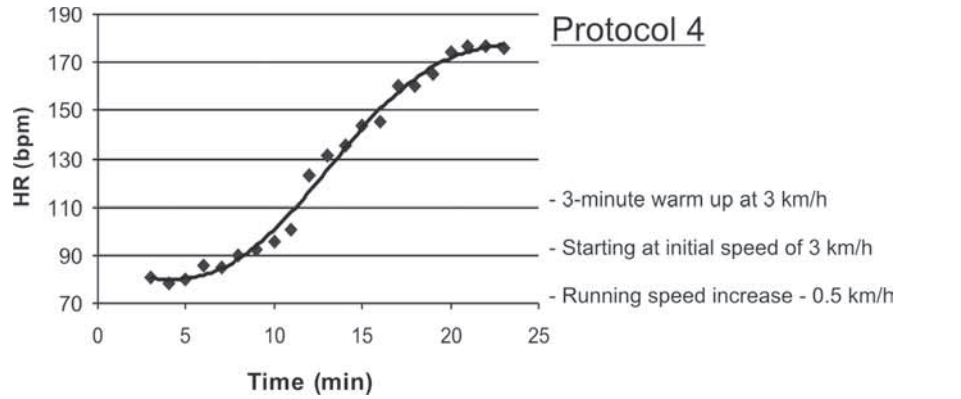

Figure 4. Original data obtained for one subject performing Protocol 4, fitted with the appropriate mathematical expression. Stage duration was constant (1 minute).

$HR=-aL^5+bL^4-cL^3+dL^2-fL+g$

where is L applied load; HR is heart rate; and a, b, c, d, f, g are parameters that define the shape of the curve.

An exponential equation (Eq. 3) fits the experimental data for the Protocol 3 (Fig. 3) with the highest correlation (R^2>0.99) :

$HR=aL^b$

where L is applied load; HR is heart rate; and a, b are parameters that define the shape of the curve.

A sigmoidal equation (Eq. 4) fits experimental data for the Protocol 4 (Fig. 4) with the highest correlation (R^2>0.98):

$$HR = y_0 + \frac{a}{1+e^{-(\frac{x-x_0}{b})}}$$

where L is applied load; HR is heart rate; and a, b, x_0, and y_0 are parameters that define the shape of the curve.

Data are presented as mean ± SE (standard error).

RESULTS

The shape of the HR-L curve depends on the exercise protocol applied.

For Protocol 1, the best fit (R^2>0.99) was achieved with Eq. 1, suggesting that the HR-L curve is linear (Fig. 1). The mean values of parameters *a* and *b* which define the shape of HR-L curve defined by the Eq. 1 are presented in Table 1.

Table 1. The mean values of the parameters that define the shape of the HR-L curve defined by Eq. 1 for Protocol 1.

a	*b*
7.32±0.56	105.2±4.5

Values given are means ± SE, n=8

For Protocol 2, the best fit (R^2>0.99) was achieved with Eq. 2, indicating that the HR-L curve is S-shaped (Fig 2). The mean values of parameters *a, b, c, d, f* and *g*, which define the shape of HR-L curve in Eq. 2, are presented in Table 2.

Table 2. The mean values of the parameters that define the shape of the HR-L curve defined by Eq. 2 for Protocol 2.

a	*b*	*c*
-3•10-3±1•10-3	0.016±0.004	-0.31±0.06
d	*f*	*g*
2.54±0.05	3.31±0.03	117±9

Values given are means ± SE, n=8

For Protocol 3, the best fit (R^2>0.99) was achieved with Eq. 3, showing that the HR-L curve is exponential (Fig 3). The mean values of parameters *a* and *b*, which define the shape of the HR-L curve in Eq. 3, are presented in Table 3.

Table 3. The mean values of the parameters that define the shape of the HR-L curve defined by Eq. 3 for Protocol 3.

a	*b*
26.87±1.7	0.66±0.04

Values presented are means ± SE, n=8

For Protocol 4, the best fit (R^2>0.98) was achieved with Eq. 4, suggesting that the HR-L curve has a sigmoidal shape (Fig 4). The mean values of parameters *a, b,* x_0 and y_0, which define the shape of the HR-L curve in Eq. 4, are presented in Table 4.

Table 3. The mean values of the parameters that define the shape of the HR-L curve defined by Eq. 3 for Protocol 3.

a	*b*	*c*	*d*
104.7±6.7	2.94±0.38	13.27±0.34	74.8±3.7

Values presented are means ± SE, n=8

DISCUSSION

Some controversy surrounds the question of HR-L curve shape. Our data clearly demonstrate that the shape of HR-L curve depends on the exercise protocol applied.

In order to evaluate the possible influence of the experimental protocol on the relationship between heart rate and applied load, the same subjects performed different incremental exercise protocols. We chose the four different laboratory treadmill protocols of increasing load that would (according to our preliminary testing) result in differently shaped HR-L curves. Indeed, the change in protocol resulted in differently shaped HR-L curves. It seems that the shape of the HR-L curve depends strongly on both the initial speed and the size of the increase in running speed, while the stage duration remains constant. Changes in the initial speed and in the size of the increase in running speed could be also included in other incremental exercise test protocols, such as cycle/ergo meter tests or the open field track test.

A moderate initial speed accompanied by smaller increases in running speed (Protocol 2, Eq. 2) resulted in S-shaped HR-L curve. Although this curve is S-shaped, it cannot be described by sigmoidal mathematical function because it is asymmetric. Instead, this curve can be described by a 4th or 5th order polynomial function.

The use of larger increases in running speed at each step in a protocol with moderate initial speed leads to a linear HR-L curve (Protocol 1, Eq. 1).

An increase in initial speed accompanied by smaller increases in running speed favoured an exponentially shaped HR-L curve (Protocol 3, Eq. 3).

Our results indicate that both the initial speed and the size of running speed increase affect the shape of the HR-L curve in protocols with constant stage duration, though these effects vary based on the individual. It is obvious that the exercise protocol must be adjusted for each individual

to yield an HR-L curve with the shape desired for further analysis. This may require the use of exercise protocols that have not been commonly used. These findings have practical implications for the types of protocols that should be applied to yield the most suitable results for further mathematical analysis.

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ACUTE AND CHRONIC APHASIA: IMPLICATIONS FOR NEUROPLASTICITY

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Although functions of brain areas are in principle localizable, the localizations of functions are not fixed, which implies that the adult human brain retains the potential for plasticity. With regard to recovery of function, the neural circuitry supporting language functions responds differently to different types of lesions. As an example, cases of low-grade gliomas affecting Broca's area (Brodmann areas 44 and 45) have been reported in which language function was later supported by areas that are typically not implicated in language, such as BAs 46 and 47. On the other hand, the literature on recovery of language following stroke contains controversies with regard to the issue of reorganization of language substrates in aphasia; there are reports of involvements of both perilesional and contralesional areas. The exact roles of these areas in language recovery after stroke are not clear at the moment, and in particular, the role of the right hemisphere in recovery has been hotly debated for years.

Furthermore, there is evidence indicating that perilesional areas are the substrate of language reorganization following smaller lesions (e.g., see Cao et al., 1999), while larger lesions typically involve contralateral homologous areas. In line with this evidence, some research has reported that language recovers better when recovery occurs within the original network than when it occurs in the contralateral hemisphere (e.g., Karbe et al., 1998). Similarly, research contrasting acute and slow-growing lesions has shown that functional compensation is considerably better following low-grade gliomas than acute stroke (Desmurget et al., 2007). If the hypothesis that brain plasticity is mediated by a gradual learning process, with plastic changes taking place via "supervised learning", is correct, then the findings on improved aphasic recovery supported by perilesional areas makes sense. Similarly, this hypothesis would explain why acute destruction, which prevents gradual learning, leads to poor recovery (Desmurget, 2007). More importantly, the hypothesis could also explain the data on "shifting" of language function from the right hemisphere to the left hemisphere once learning, i.e. recovery, is relatively complete.

The differences in mechanisms of language recovery after stroke in acute and chronic aphasias have not yet been thoroughly investigated, despite recent methodological advances that allow such research, including the availability of functional neuroimaging and external brain stimulation techniques. Until recently, patterns of language recovery after stroke were typically studied in chronic aphasia (Cramer & Riley, 2008). However, cases of acute aphasia are more informative about language recovery processes. Additionally, studying acute aphasia is important because early intervention is essential. Unlike structural imaging methods (e.g., computerized tomography (CT) and magnetic resonance imagining (MRI)), which lack the potential to capture plastic changes in the brain, functional neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) yield insights on preservation of function, thereby contributing to our understanding of the organizational flexibility of the human brain. More importantly, functional neuroimaging allows us to study temporal patterns in recovery of language function in aphasia, which may help to resolve the current controversy on the role of contralesional areas in recovery. One step towards a better understanding of the mechanisms of language recovery after stroke, including the patterns of reorganization and the roles of the perilesional and contralesional areas in these patterns, would be to collect data at different post-stroke temporal points, such as acute, subacute, and chronic.

Recently, Saur and collagues (2006) have shown that the patterns of reorganization differ at distinct phases of post-stroke recovery of language. More specifically, they have proposed that the acute phase is associated with little perilesional activation; the subacute phase is associated with activation of homologous areas in the right hemisphere, while in the chronic phase, a re-shifting to the language

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areas of the left hemisphere is associated with further language improvements. According to this model, activation of the right hemispheric areas in a chronic aphasic patient indicates a poor recovery.

While Saur et al.'s model nicely explains their data, it requires further testing. It also raises some interesting questions. For example, do changes in activation patterns amongst the three distinct post-stroke temporal points indeed arise from plasticity (as opposed to, for example, arising from resolution of diaschisis (Hillis, 2006), and why does progress in language recovery after stroke seems to require changes in lateralization? How are the mechanisms that support language in aphasic patients who recover well different from the mechanisms in patients with similar lesions who fail to recover?

The answers to questions like these are relevant not only for gaining further insights into the functional architecture of language and into neuroplasticity in general, but also for treatment of aphasia. Given the high incidence of stroke in many countries, its steady increase in causing disability, and a general need for improvement of aphasia treatments, these answers are important.

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LANGERHANS CELL HISTIOCYTOSIS OF THE TEMPORAL BONE

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HISTIOCITOZA LANGERHANSOVIH ĆELIJA TEMPORALNE KOSTI

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a disease of unknown etiology which is characterized by the pathological proliferation of Langerhans cells in various organs. The incidence of Langerhans cell histiocytosis in the adult population is approximately one to two cases per million, and presentation ranges from 15 to 91 years old. Although this disease may arise in various tissues such as the skin, hypothalamus, liver, lung, or lymphoid tissues, it most frequently occurs in the head and neck. The diagnosis is obtained by evaluating the patient's clinical presentation, radiographic imaging, and biopsy results. The most frequent radiological patterns observed are osteolytic lesions, periosteal reactions, and soft tissue masses. Since LCH manifests radiologically in different ways, its diagnosis should be first suspected by the radiologist and then confirmed by immunohistochemical analysis. In this case study, the patient is a 47 year old male presenting with isolated LCH of the left temporal bone. The patient described a history of pain in the left ear and mild deafness over the past three months. Radiographic imaging confirmed mastoid bone destruction with an expanding soft tissue mass infiltrating the dura of the medial and hind skull pit, without penetration into the endocranium, middle ear, or cavum tympani. Langerhans cell histiocytosis was later confirmed by immunohistochemical analysis.

Key words: *Langerhans cell histiocytosis, temporal bone*

SAŽETAK

Hisiocitoza Langerhansovih ćelija je retka bolest nepoznate etiologije koju karakteriše proliferacija patoloških Langerhansovih ćelija u različitim organima. Incidenca bolesti je jedan do dva na milion u odrasloj populaciji. Iako se bolest može naći u različitim tkivima: koža, hipotalamus, jetra, pluća, limfno tkivo, kost je najčešće zahvaćena, a glava i vrat su najčešća lokalizacija. Dijagnoza se postavlja na osnovu kliničke slike, radioloških nalaza i biopsije. Najčešći radiološki nalaz je osteolitička lezija, periostalna reakcija i meko tkivna masa. Uprkos nekoliko radioloških manifetacija, njenu dijagnozu bi trebalo da postavi radiolog, a definitivno potvrdi imunohistohemijska analiza. Prikazan je pacijent muškog pola, star 47 godina sa izolovanom LCH leve temporalne kosti. Istorija bolesti duga tri meseca sa bolom u levom uvu i nagluvošću. Radiološki utvrđena destrukcija kosti mastoida sa ekspanzivnom meko tkivnom masom koja infiltriše duru srednje i zadnje lobanjske jame, bez prodora u endokranijum, unutrašnje uvo i cavum tympani. Imunohistohemujski utvrđena Hisiocitoza Langerhansovih ćelija .

Ključne reči: *Histiocitoza Langerhansovih ćelija, temporalna kost*

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INTRODUCTION

Langerhans cell histiocytosis (LCH) is a disease of unknown etiology, which is characterized by the pathologic proliferation of Langerhans cells in various organs. In 1953, Lichtenstein observed cytoplasmic bodies, known as X bodies, within the histiocytes of tissues from patients suffering from eosinophilic granulomas, Hand-Schuller-Christian disease, and Abt-Letterer-Siwe disease. The incidence of LCH is slightly greater in males and generally presents in childhood. The incidence of LCH in the adult population is between one to two cases per million, and the prevalence appears to be higher among caucasians. Although this disease may arise in various tissues such as the skin, hypothalamus, liver, lung, or lymphoid tissue, it most frequently occurs in the bones. Specifically, LCH occurs most commonly in the head and neck; the skull is involved in 50% of cases, the temporal bone, meatal skin, and cervical lymph nodes in 20-25% of cases, and the maxillary and mandibular bones in 5 to 10% of cases (1, 2, 3).

The pathogenesis of LCH is not well understood, and there is an ongoing debate over whether this is a reactive or a neoplastic process. Arguments supporting the reactive nature of LCH include spontaneous remission, the failure to detect aneuploidy, metaphase and karyotypic abnormalities, and a promising survival rate in patients without organ dysfunction. On the other hand, the infiltration of organs by aberrant cells, potentially lethal disease progression, and successful treatment with cancer-based modalities are consistent with a neoplastic process. Furthermore, evidence exists for a role of immune dysfunction in the pathogenesis of LCH.

The clinical picture of LCH in young adults typically consists of solitary calvarial lesions, most frequently in the skull. Other sites of involvement include the vertebra, rib, mandible, femur, ilium, and scapula. Lesions are usually asymptomatic, but bone pain may occur. When the calvarial lesions extend into the nervous system, a variety of neurological manifestations may be observed. For example, bony lesions may promote middle ear inflammatory processes combined with mastoid destruction.

The diagnosis of LCH is obtained by examining the patient's clinical presentation, radiographic imaging, and biopsy, and by detecting Birbeck granules in the lesion cells using electron microscopy. Alternatives to diagnosis include positive staining for CD1a antigen on the surface of lesional cells, S-100 protein analysis, and adenosinetriphosphatase assays (4, 5).

The treatment of LCH depends upon the combination of clinical findings. Solitary bone lesions are treated by excision; painful bone lesions may require intralesional steroid injections; and polyostotic bone lesions are best treated using systemic steroids. Lesions that are unusually large and/or painful and occur in inaccessible sites or are involved in vital structures may require radiation (3-6 Gy) for treatment. Localized skin disease is best treated with topical steroids.

More than one half of patients younger than two years of age with disseminated LCH and organ dysfunction will die of the disease, whereas the outcome in the adult population is generally promising due to slow disease progression and favourable response to treatment. However, elderly patients and patients with chronic disease typically do not respond well to treatment. LCH is further complicated by an unpredictable course of progression; however, if additional lesions do not appear within one year following treatment, the later development of such lesions is unlikely (6).

CASE STUDY

Patient J.M. was a 47 year old male who was admitted to the clinic on November 10, 2008 (medical history number 40968). He presented with diminished hearing in the left ear, pain in the left ear region, humming in the left ear, and occasional vertigo. The patient's condition had been diagnosed three months prior to admission and was characterized by pain in the left ear, diminished hearing in the left ear, and vertigo. Upon admission to the clinic he received treatment for otitis externa as well as vertigo. The patient's symptoms improved, however slight deafness and pain in his left ear persisted.

Upon clinical examination it was determined that the patient had palpatory sensitivity to pain over the retroarticular region of the left ear, and that the bony external auditory channel had narrowed and the upper wall brought down, with no visible perforation of the ear drum. The patient's clinical findings included the following:

Audiometric findings: mixed, average-to-severe hearing damage in left ear and normal results in the right ear.

Tympanometry: normal findings, bilateral curve A.

Laboratory results: measurements within normal range except SE 26 and CRP 13.30.

Mastoid radiography: mastoid cell destruction with formation of a confluent hole in the left mastoid.

Mastoid CT: soft tissue mass in the left mastoid filling the mastoid hole but not covering the cavum tympani. There is destruction present in the out er mastoid wall, mastoid tegmen, and sigmoid sinus toward the hind skull pit (pictures 1 and 2).

MR: soft tissue mass destruction of the temporal bone (mastoid) which is natively heterogenic in appearance with no evident spreading to the middle ear or cavum tympani. After administration of contrast-intensive T1W, a significant signal increase in the tumor was observed. Mastoid roof bone destruction and the posterior-base segment of the temporal part of the brain significantly correlated with the dura, which was suspected to be infiltrated in the absence of penetration into the endocranium. Bone destruction was observed toward the hind skull pit with suspected dural infiltration. The left sigmoid sinus was narrowed compared to the right, and blood flow had slowed down through this sinus (pictures 3 and 4). Lungs Rtg normal.

A mastoidectomy was performed as well as a biopsy at a different health care institution, and tissue was sent for pathohistological and immunoistiochemical examination. Pathology studies eventually confirming Langerhans cell histiocytosis, characterized by eosinophilia between tumor cells and S100 protein- and CD1a-positive tumor cells.

DISCUSSION

The signs and symptoms of otologic histiocytosis may mimic those of acute or chronic infectious ear disease (7). In Langerhans cell histiocytosis, the temporal bone is typically involved and appears on radiographs as extensive lytic lesions associated with soft-tissue masses (8).

The first diagnostic test typically performed for LCH is the plain radiograph; however, the radiological findings may be difficult to analyze and may mirror many other pathologies. The most frequent symptom associated with LCH is pain, and the most common radiological manifestations are primarily osteolytic lesions (45 out of 59 patients). Periostal reactions and soft tissue masses were also found in 30% of patients. Despite the fact that LCH may be difficult to diagnose radiologically, it should at least be suspected by the radiologist when the abovementioned signs are observed (9).

In our case study, the first symptom reported by the patient was pain, and subsequent otoscopy demonstrated narrowing of the external auditory channel. This narrowing consequently leads to otoneurological symptoms, including deafness, vertigo, loss of balance when walking, as well as pain in the mastoid region and palapatory mastoid sensitivity. Laboratory findings in our case study were within normal, with the exceptions of SE(26) and CRP(13.30). Mastoid radiography was performed and showed significant mastoid cell destruction forming a confluent hole in the left mastoid region. After performing CT and MR scans, serious mastoid destruction accompanied by tegmen and bone destruction around the sigmoid sinus with soft tissue masses was observed, and this was accompanied by infiltration into the dura of the medial and back skull pit. Involvement of the endocranium, middle ear, and cavum tympani was not observed. Following injection of contrast, there was a significant increase in T1W signal in the region of the tumor, allowing for exclusion of holesteatoma from the differential diagnosis. The patient's clinical presentation was not suggestive of osteomielitis, and the patient was in overall good condition. The patient showed no signs of enlarged lymph nodes, serious bone destruction, or extensive soft tissue masses, thus malignant disease was not suspected. A final diagnostic biopsy was required to determine the exact patohistiological and immunohistochemical status.

Currently there have been no controlled studies in the literature establishing the optimal treatment protocol for LCH. The prognosis for LCH in adults is generally good due to the slow progression of the disease and its favourable response to treatment. The treatment of LCH is controversial, particularly when dealing with localized LCH in the head and neck. Many researchers believe that surgery alone is too invasive in such cases. However, most clinicians recommend surgical intervention associated with some other form of treatment such as corticosteroid therapy, chemotherapy, or radiotherapy on focal lesions. Multifocal lesions, however, require more aggressive therapeutic approaches (7,10).

Once initial bone imaging and radiological analyses have been performed to determine the stage of disease, additional analyses should be obtained every six months for the next three years. If additional lesions do not appear within one year, the development of such lesions over time becomes highly unlikely. Full recovery is expected in cases of single lymph node involvement or isolated skin lesions; however, lesions that are unusually large and painful or occur in inaccessible sites or vital structures may require radiation (3-6 Gy).

Complications of treatment occur in 30-50% of LCH patients. For example, patients with multisystemic disease, craniofacial involvement, chronic LCH, or disease reactivation may be at higher risk of developing diabetes insipidus over time (4).

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CORRECTIONS

TO OUR READERS

I am using this opportunity to inform the readership about changes in status of the book "Clinical Pharmacy" (in Serbian) by Vesela Radonjic and Slobodan Jankovic, that was presented in Volume 9, No2, 2008 issue of this journal, under the section "New books". Due to large number of technical errors made during processing of this publication (which were recognized after printing of the book), it became useless for the readers. Therefore, in November 2008 this book was withdrawn by the publisher, and does not figure out as publication any more. The authors are working on the new manuscript which should appear in the future, after new editing and publishing process is finished.

Prof. Slobodan Jankovic,
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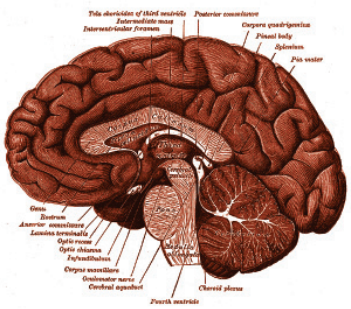

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