

SUMMARY

MOLECULAR ASPECTS OF APOPTOSIS

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Corresponding to its importance in cell count homeostasis in the body, apoptosis is a tightly regulated phenomenon. Both extracellular and intracellular molecules provide multiple regulatory and counter-regulatory pathways. Cell death is usually a response to the cell microenvironment, where the absence of certain factors (survival factors) or the presence of lethal factors promotes apoptosis. Surrounding cells, soluble mediators and the extracellular matrix regulate cell death and survival. Surrounding cells can synthesize survival or lethal factors. The intracellular regulation of apoptosis is also one of the forefront fields in biomedicine research. During the past five years, tremendous progress has been made in understanding apoptosis as a result of molecular identification of the key components of this intracellular suicide program. Biochemical activation of these key components of the cell death program is responsible for the morphological changes observed in apoptosis, including mitochondrial damage, nuclear membrane breakdown, DNA fragmentation, chromatin condensation and the formation of apoptotic bodies. Caspase activation plays a central role in the execution of apoptosis. Most caspases are constitutively expressed as inactive proenzymes (procaspases) in the cytosol and according to some reports in the mitochondria. Caspases are sequentially activated by proteolysis during apoptosis. In this review, we focus on the biochemical pathways that control caspase activation, particularly the activation pathways that are initiated by cell surface death receptors and mitochondria.

Key words: cell death, apoptosis, caspase, cell surface death receptor, mitochondria

SUMMARY

HIP FRACTURE — PERSONAL, FAMILY AND SOCIAL PROBLEM OF THE THIRD AGE

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Aim: The percentage of elderly people increases in societies today and so does the number of specific conditions, illnesses and injuries, with hip fracture as the most important one. The aim of the study was to point to hip fracture as a medical and social problem by objectively quantifying functional abilities of geriatric patients after hip fracture.

Patients and Methods: The study included 414 (63 male and 351 female) with femoral neck fracture and hip endoprosthesis implanted at University Department of Traumatology in Ljubljana during the 1988–2004 period. Data on sex distribution, concomitant diseases, complications, estimation of functionality before injury, and dynamic and final level of functional recovery were collected.

Results: The patient mean age was 77 ± 7.3 (range 28–96) years. Excellent mobility before injury, according to personal report, was recorded in 322 (77.78%), good mobility in 78 (18.84%) and poor mobility in only 14 (3.38%) patients. The mean dynamics of functional recovery was as follows: independent sitting at 2 days, standing at 3.6 days, and walking at 7 days of the surgery. At the end of rehabilitation, an average patient felt periodic pain that did not affect his/her activities, could walk without problems at least one kilometer, limped to a certain degree, used a cane, could climb stairs holding a handrail, sat in the chair for a long time, put on shoes and socks with minor difficulties, used public transportation and had no significant deformity of the hip. With that level of functionality, our patients were independent in daily activities, able to stay socially integrated, and other people's help was reduced to the minimum.

Discussion: The patient's functionality before injury, the duration and quality of rehabilitation after surgery, and the patient's motivation and cooperation during rehabilitation are the key factors of patient recovery to the pre-injury state. In spite of numerous concomitant diseases, reduced psychophysical abilities of the elderly and medical difficulties in the management of these injuries, such treatment of hip fractures is necessary and human for patients and time-consuming for medical staff, yet being the most profitable option for the society. Hip fracture and consequential disablement cause a double problem. On the one hand, it entails dependence on other person, family or social institution, or society in general, and on the other hand there is mental frustration, especially if he/she is psychically instable. Quite frequently, disabled persons have psychical traumas that have unfavorable impact on their families. It is additionally complicated in societies that tend to stigmatization of disabled persons. Therefore, it is very important how the society will behave toward disabled elderly who are generally more vulnerable.

Key words: hip fracture, society, gerontology, functionality

SUMMARY

PROTEINASE EXCRETION ABILITY OF *CANDIDA ALBICANS* SPECIES

ISOLATES IN CLINICAL SPECIMENS

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Aim: The aim of the study was to establish whether the *Candida (C.) albicans* species isolates from samples of the patient digestive, respiratory and genitourinary systems differed in the ability of proteinase excretion.

Methods: A total of 1009 isolates of the *C. albicans* species obtained from 1009 clinical specimens of the digestive, respiratory and genitourinary systems of 666 patients were examined. All samples were inoculated onto Sabourauds glucose agar and incubated aerobically at 37 °C for 3–7 days. Identification of *C. albicans* was done by standard and commercial tests. To test the proteinase excretion ability, we employed the Odds and Abbott method. The isolates were inoculated on a culture medium containing agar, glucose, vitamins and beef albumin fraction V (pH=3.2), and stored for 7 days at 30 °C. Each isolate was tested twice, with the results read by the same person. Development of thready colonies in a milky–white field was considered as positive finding. Study results are shown in easy-to–consult tables. Distribution differences were assessed by χ^2 –test.

Results: Of 1009 *C. albicans* species isolates obtained from clinical specimens, 695 (68.9%) had the proteinase excreting ability. The presence of this enzyme was demonstrated in 72.7% of the species isolates obtained from samples of the digestive system, 65.8% of isolates from respiratory system and 59.6% of isolates from genitourinary system. Analysis of χ^2 –test results showed no statistically significant difference in the ability of *C. albicans* species isolates from specimens obtained from digestive, respiratory and genitourinary systems to excrete proteinase.

Discussion: The results of the present study are in agreement with the results of most other researchers reporting on the proteinase excreting ability to be demonstrated in 40%–80% of *C. albicans* isolates. In the present study, the ability to excrete proteinase was demonstrated in 68.9% of *C. albicans* species isolates obtained from clinical samples.

Conclusion: The ability to excrete proteinase was demonstrated in 59.6%–72.7% of *C. albicans* species isolates obtained from the patient digestive, respiratory and genitourinary systems. Analysis of the results yielded no statistically significant difference in the proteinase excreting ability among the isolates obtained from digestive, respiratory and genitourinary systems.

Key words: *Candida albicans*, proteinase, digestive, respiratory and genitourinary systems

SUMMARY

EXPRESSION OF BCL–2, KI–67 AND P–53 IN UVEAL MELANOMAS

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Aim: To investigate expression of proliferative markers bcl–2, Ki–67 and p–53 immunocomplexes in uveal melanoma cells; and to establish whether the intensity of expression correlates with the pathological level of invasion (pT), which would result in prognostic significance.

Methods: Thirty cases of primary uveal melanomas of two different levels of invasion (pT2 and pT3); indirect PAP immunoenzyme method and three step ABC/AP method. The intensity of the reaction was evaluated by a semiquantitative method as negative (–), weakly positive (+), modestly positive (++) and strongly positive (+++). Results were statistically analyzed by Fisher exact test for small examples.

Results: The reactivity of Ki–67 and p–53 protein was markedly stronger than bcl–2 in pT2 and pT3 stages. p–53 protein expression showed similar distribution for Ki–67 protein according to pT stages.

Conclusion: The reactivity of all three markers was stronger in pT3 stage, especially of proliferation markers Ki–67 and p–53. In addition to the fact that they both are reliable indicators of the metastatic potential, Ki–67 is a better marker because there is a well established technique for measuring cell proliferation in all phases of the cell cycle.

Key words: bcl–2 oncoprotein, Ki–67 oncogene, p–53 suppressor gene, melanocyte proliferation, uveal melanoma, tumor markers

SUMMARY

SPECIFICITY OF HYPERGLYCEMIA TREATMENT IN ACUTE STROKE PATIENTS

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Introduction: Although most of clinical studies suggest that hyperglycemia is associated with poor clinical outcome in acute stroke patients, there still are many theoretical and practical doubts that are reflected in some differences in treatment recommendations from clinical guidelines developed in Europe (European Stroke Initiative, Croatian Association for Neurovascular Disorders) and in the USA (American Stroke Association).

Purpose: To point to the most important acts and doubts related to the acute treatment of hyperglycemia in stroke patients.

Methods: On literature review, the following databases were used: Medline (1976–2006), National Guideline Clearinghouse and Stroke Trials Registry–Internet Stroke Center. Selection of the articles depended on clinical experience and knowledge of the authors.

Results: The most important facts indicating a high prevalence of glucose regulation disturbances in stroke patients are highlighted, along with data on the reactive and iatrogenic pathophysiological mechanisms leading to hyperglycemia. Literature data that undoubtedly suggest an association of hyperglycemia with poor clinical outcome and the unfavorable effect of hyperglycemia on the outcome of thrombolysis are pointed out. Some contradictory data on the postulated pathophysiological mechanisms by which hyperglycemia causes cerebral damage are reviewed, especially regarding the role of tissue lactic acidosis induced by hyperglycemia. The favorable results of insulin therapy in critically ill patients are presented, along with the fact that there is still no definitive evidence that strict control of hyperglycemia can improve the outcome in stroke patients.

Discussion: At present, it is not possible to claim whether hyperglycemia contributes to the poor outcome of acute stroke as an independent factor or it is just a marker of the disease severity. It seems that the unfavorable effect of hyperglycemia is not only associated with the level of the brain lactic acidosis. Rather, a complex interaction of several different mechanisms appears to be involved. The threshold of blood glucose concentration at which it becomes a predictor of unfavorable outcome has not yet been exactly established. The different levels of hyperglycemia recommended to be treated with insulin partly reflect different evaluation of the guidelines regarding the potential risks of insulin-induced hypoglycemia and further iatrogenic metabolic disorders. It might be expected that the results of ongoing randomized controlled trials should contribute to developing of more precise and more harmonized clinical guidelines for the treatment of hyperglycemia in stroke patients.

Key words: stroke, hyperglycemia, clinical guidelines, insulin therapy

SUMMARY

EXPERT MEDICAL WITNESS TESTIMONY OF MAXILLOFACIAL INJURIES

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The basic principles of expert medical witness testimony of the maxillofacial region are described. The specific anatomic characteristics of the region are emphasized, especially in view of the fact that face is the most exposed part of the human body. Post-traumatic deformities of the maxillofacial region involve soft tissues of the face and mouth as well as bony structures of the viscerocranium and teeth. Endured physical pain, lessening of life activities, disfigurement and requirement of assistance by third person are separately described as an important part of expert medical witness testimony of the maxillofacial region. The number of lawsuits raised against physicians has significantly increased in the past several years, more often in cases where the patients are dissatisfied with the results of cosmetic surgery, especially when these procedures are performed on the face.

Key words: expert medical witness testimony, injury, maxillofacial region, post-traumatic deformity, face

SUMMARY

REGULATORY ASPECTS AND RECOMMENDATIONS RELATED TO LEGIONNAIRES' DISEASE CONTROL IN CROATIA

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Health concerns related to Legionnaires' disease have been identified as an area of increasing public and professional interest. Any natural water or man-made water systems worldwide may be reservoirs of legionellae. That is one of the reasons why development of specific legislation on legionellae prevention is such a complex problem. Nevertheless, industrialized countries in the world and in Europe have appropriate legislation that is subject to continuous improving. In the European Union member countries, attention has been increasingly focused on travel associated Legionnaires' disease. In Croatia, the By-Law on Infectious Disease Protection is the basic legal act related to the prevention of infectious diseases including Legionnaires' disease. Arrays of preventive measures that can apply to hotels, public sites and buildings as potential places of exposure to legionellae have been recommended. In Croatia, the epidemiological situation concerning Legionnaires' disease is more favorable than in many European countries and should be maintained and improved through legislation and good practice.

Key words: Legionnaires' disease, legislation, prevention

SUMMARY

CAUSES OF CLIMATIC CHANGES AND THEIR CONSEQUENCES ON HUMAN HEALTH

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Environmental disasters are common phenomena caused by human factors. Disaster episodes may be the result of climatic changes such as global warming, which can lead to floods or drought. Greenhouse gases, and especially the ozone, represent a special problem. Atmospheric pollutions are the result of fire, storm dusts, winds, acid rain, etc. Underwater earthquakes very often end in tsunami with waves of up to 30 meters. Disasters described in the territory of Croatia include atmospheric pollutions, fires, floods, and droughts. All disasters affect the health of the population, particularly of the elderly. This most often includes the cardiovascular and respiratory systems, allergic reactions, and carcinogenic effects, resulting in increased mortality.

Key words: environmental disasters, unfavourable climatic changes, causes of disasters, health effects

SUMMARY

SURGICAL TREATMENT OF LOWER JAW PSEUDOARTHROSIS AS A RESULT OF FRACTURE NON– TREATMENT FOLLOWING TOOTH EXTRACTION

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Fracture of the lower jaw following tooth extraction is a rare and severe complication, occurring most often in the preangular region following third molar extraction. When left untreated, pseudoarthrosis can occur. Symptoms show a wide variance, including pathologic mobility, pain and infection, as well as sometimes trismus before and following surgical treatment. The possible complications of pseudoarthrosis may be malnutrition, jaw deformity and long–term disability. Treatment options range from prescription of a soft diet in case of simple fracture to surgical treatment by open reduction and internal fixation. A case is presented where a 47–year–old male suffered from painful perimandibular swelling and complained of »instability« of the lower jaw as well as hypoesthesia in the area of the left mental nerve. Case history revealed that he had had extraction of the lower left second molar (tooth 37) four months before. Following clinical and radiographic examination he was diagnosed with non–diagnosed and/or non–treated lower jaw fracture. The patient was surgically treated using an oseosynthetic plate to ensure stability. The postoperative protocol showed satisfactory results. Bone growth in the fracture line was recorded in the follow up. However, due to the four–month period of pseudoarthrosis and infection, the plate was removed much later than it would have been the case if surgical treatment had been performed immediately following the fracture. The delayed diagnosis of this fracture demonstrates the necessity of radiologic control when a fracture is suspected following tooth extraction. When a patient shows symptoms inconsistent with those following tooth extraction, surgical consultation is recommended.

Key words: pseudoarthrosis, lower jaw fracture, tooth extraction, complication

SUMMARY

THE OUTBREAK OF ACUTE GASTROENTERITIS CAUSED BY NORWALK LIKE VIRUSES IN ZADAR GENERAL HOSPITAL (2007)

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Objective: Early detection of clinical signs and symptoms of acute gastroenteritis and appropriate preventive measures to stop the spread of infection.

Methods: Epidemiological inspection, clinical examination of hospitalized patients followed by standard bacteriologic and virologic analysis. Norovirus antigen was detected in stool specimen by enzyme immunoassay (EIA).

Results: An epidemic of acute gastroenteritis caused by Norwalk like viruses lasted for two weeks (January 26 — February 9, 2007). A total of 39 cases were recorded, including 22 (56.4%) inpatients and 17 (43.6%) healthcare workers with disease symptoms. All patients (n=22; 100%) were hospitalized at Department of Internal Medicine, Cardiology Ward; 11 (64.7%) healthcare workers were working at Cardiology Ward, 3 (17.6%) at Diagnostic Cardiology Laboratory where patients underwent their diagnostic procedures, and 1 (5.9%) healthcare worker at Department of Anesthesiology and Intensive Care was patient consultant at Cardiac Intensive Care Unit. Other

healthcare workers, 1 (5.9%) from Department of Neurosurgery and Department of Pathology each, were in family contact with two health care workers employed at Cardiology Ward.

Discussion: The Hospital Infection Control Committee was informed about the outbreak of acute gastroenteritis on day 8 of the outbreak. Anti-epidemic measures (according to the source of infection detected and to the mechanisms of transmission) were implemented after epidemiological inspection on day 1 of event recording and continued for two more weeks after the occurrence of the disease clinical symptoms in the last patient involved.

Conclusion: It is necessary to promptly inform the Hospital Infection Control Committee on the epidemic outbreak for effective and timely anti-epidemic measures to stop the spread of acute gastroenteritis caused by Norwalk like viruses.

Key words: outbreak, norovirus, anti-epidemic measures

SUMMARY

ACUTE RHABDOMYOLYSIS: A CASE REPORT AND LITERATURE REVIEW

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Acute rhabdomyolysis is a syndrome characterized by the lesion of skeletal muscle resulting in subsequent release of intracellular contents into the circulatory system, which can cause potentially lethal complications. These contents include myoglobin, creatine phosphokinase, potassium, aldolase, lactate dehydrogenase and glutamic-oxaloacetic transaminase. There are numerous causes that can lead to acute rhabdomyolysis and many of patients present with multiple causes. The most common potentially lethal complication of rhabdomyolysis is acute renal failure. In this article we present a case of a patient that developed clinical signs of acute rhabdomyolysis after consumption of heroin and alcohol. After approximately nine hours of alcohol and heroin induced coma he had acute compartment syndrome of the right arm, and clinical and laboratory signs of acute rhabdomyolysis with acute renal failure as a complication of rhabdomyolysis. Acute rhabdomyolysis developed in the patient as the result of acute compartment syndrome, with direct toxic activity of alcohol and diamorphine. During the period of coma, due to lying in particular position over a long period of time, pressure upon the certain part of the body caused muscle compression and capillary occlusion in fascial compartments, which led to ischemia. Upon pressure relief and beginning of tissue recovery, post ischemic compartment syndrome occurred with subsequent rhabdomyolysis. Getting out of coma the patient started to complain of severe pain in the right arm, which clinically worsened on passive stretching of the limb, with the loss of sensation and weakness. Laboratory findings showed high levels of creatine phosphokinase as the most sensitive marker of muscular damage. The peak of creatine phosphokinase level can be predictive for the development of acute renal failure because myoglobin level may return to normal within 6 hours after muscle injury. The peak of creatine phosphokinase (186 080 U/L; normal range 0-177) was recorded at 12 hours of admission. Other pertinent laboratory results such as urea, creatinine, prothrombin time, alanine aminotransferase and aspartate aminotransferase were also changed significantly. The peak of potassium level before dialysis was 6.8 mmol/L. Emergency fasciotomy of the anterior and posterior compartment syndrome was performed by a team of physicians after clinical examination. The second look debridement was performed at 48 and 72 hours. The plastic surgical procedure was performed 4 weeks later. On admission the patient also had oliguria with dark brown pigment in his urine. Arterial blood gases revealed metabolic and respiratory acidosis. The patient was hypovolemic and IV rehydration with crystalloids, sodium bicarbonate and mannitol started immediately upon admission. Despite therapy his urine output decreased. Hemodialysis was initiated at serum potassium level of 6.8 mmol/L and continued until his urine output returned to normal in three weeks. The patient was discharged from the hospital after six weeks, with normal urine output, without functional abnormality in his upper right limb.

Acute rhabdomyolysis should be considered as a possibility in any patient with prolonged immobilization while in coma as well as in any intoxicated patient. Of course, creatine phosphokinase is the most sensitive indicator of muscle injury and the degree of creatine phosphokinase elevation correlates with the amount of muscle injury and disease severity. Other laboratory findings can help identify common complications of rhabdomyolysis such as acute renal failure, metabolic derangements and disseminated intravascular coagulopathy.

Key words: acute rhabdomyolysis, compartment syndrome, acute renal failure, coma

SUMMARY

PHARMACISTS AND PHARMACIES IN BJELOVAR IN THE 18th-19th CENTURIES

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Previously unknown data on the historical development of pharmacist service in Bjelovar, retrieved from registers of births, marriages and deaths, and from some published material are presented. In Bjelovar, the development of pharmacist service proceeded in parallel with foundation of the town of Bjelovar in the second half of the 18th century, with opening of the first pharmacy in 1768 and second, municipal pharmacy in 1780, along with the activity of initially military and later civilian pharmacists (*Simon Peschowar, Josephus de Blüweis, Franz Antonius Bretner, Martinus Mathias Birker*). Another pharmacy was opened in 1826; two pharmacies and pharmacists were continuously working during the 19th century (*Antonio Eisenlaitner (Aisthleitner), Georg Valentovich, Kolman German, Josip Werklein, Vjekoslav pl. Dolovačak, Vilim Luterotti*). In addition to scant known information, some

new socio–historical data on Bjelovar pharmacists and their families are presented.

Key words: history, pharmacy, pharmacists, pharmacies, Bjelovar, 18th and 19th century

SUMMARY

AMUSIA AND APHASIA OF BOLÉRO'S CREATOR — INFLUENCE OF THE RIGHT HEMISPHERE ON MUSIC

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Objectives: The experience with cortical localization (BA 44, 45, 22) of language (Broca, Wernicke and others) in the left hemisphere has been repeatedly tested over the last 150 years and is now generally accepted. A single case report with autopsy findings (Leborgne, Tan tan), has enabled to localize the seat of spoken language in the left third frontal convolution. As music and language have a lot in common and even share the same hearing system, it is logical to try to localize the cognitive centers for music too.

Methods: The disabling neurological disease illness of Maurice Ravel (1875–1937), a French impressionist composer, is not the right example to localize music center as that of Broca's language center, but it demonstrates the role of the right hemisphere in music production. In the last five years of his life, Ravel suffered from an unknown disease that affected the left hemisphere causing aphasia, apraxia, alexia, agraphia and amusia. It was the reason why Ravel could not compose during the last years of his life. In contrast to Ravel, Shostakovich and Britten continued writing music works of their own although aphasic after having sustained two strokes to the left hemisphere. While lacking clinical cases with selective ablative brain lesions, research into the music localization can be done using modern imaging technologies such as fMRI and PET.

Results: Exercising music (professionally) develops analytical process in the left hemisphere whereas other individuals process music in their right hemisphere. There is right ear (left hemisphere) predominance in musicians and *vice versa* in musical amateurs. Music lateralization towards the right hemisphere is seen in women and in inattentive listeners. It can be subject to cultural influence, so the Japanese process their traditional popular music in the left hemisphere, whereas Westerners process the same music in the right hemisphere. Music and language are processed separately; they are localized in homologous regions of the opposite hemispheres. In 1937, Ravel underwent neurosurgical procedure performed by Vincent; autopsy was not done. It is believed that the cause of his disease was primary progressive aphasia associated with Pick's disease.

Conclusion: Boléro and Concerto for the Left Hand were the last Ravel's works (the onset of his disease), so it is possible that they projected the influence of the healthy right hemisphere onto his music (and on the creative process) because Ravel's left hemisphere was damaged. Indeed, in these last music works one can feel the predominance of changes in pitch (timbre), i. e. right hemisphere, in comparison to only few changes of melody (left hemisphere).

Key words: Maurice Ravel, amusia, primary progressive aphasia, Pick's disease, specialization of brain hemisphere