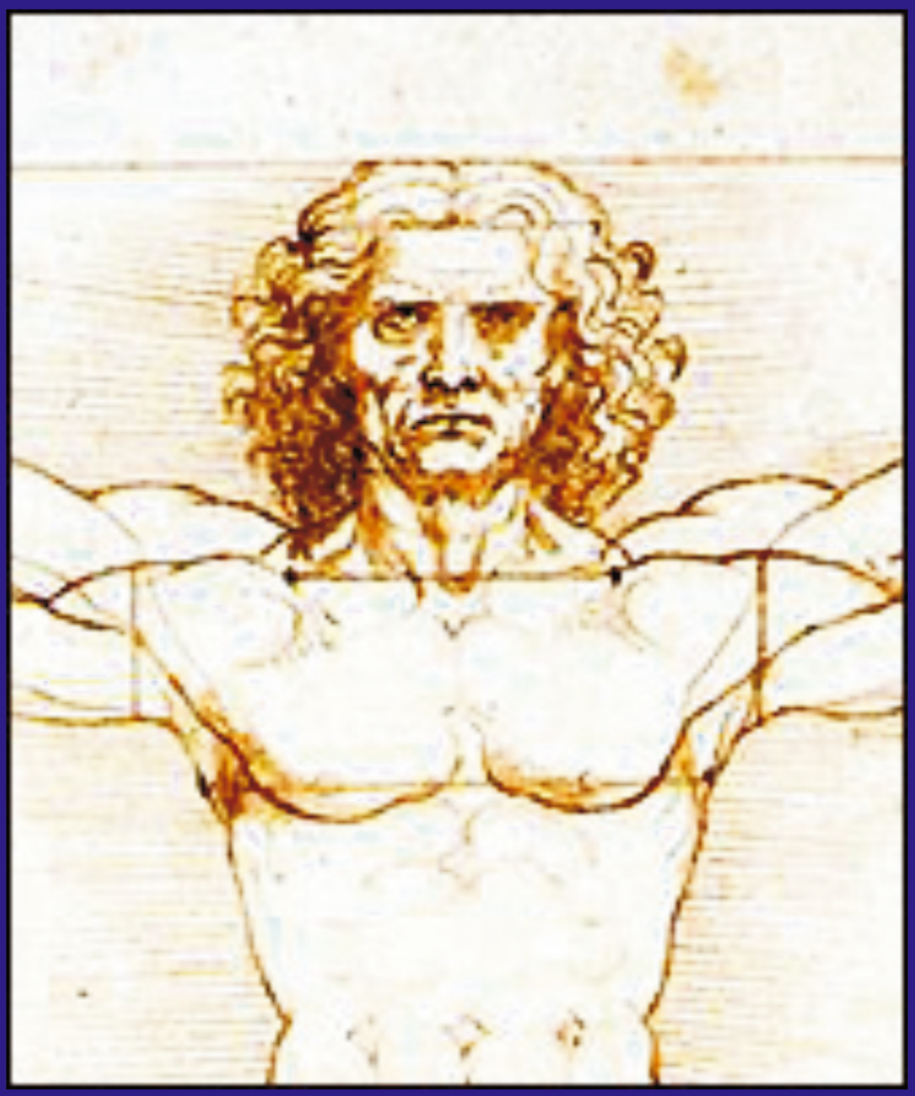
SANAMED

ISSN-1452-662X



Vol 14 (2) 2019.

MEDICAL JOURNAL

SANAMED

ISSN-1452-662X

Izdavač

Udruženje lekara Sanamed, Novi Pazar

ČASOPIS IZLAZI TRI PUTA GODIŠNJE

Adresa uredništva

„SANAMED“, Ul. Palih boraca 52, 36300 Novi Pazar, Srbija
email: sanamednp2006@gmail.com, www.sanamed.rs

Štampa

„OFSET“, Kraljevo

Tiraž

500

Pretplata

Godišnja pretplata: 4500 din. za domaće ustanove; 1500 din. za pojedince; za inostranstvo 75 eura (u dinarskoj protivrednosti po kursu na dan uplate). Pretplatu vršiti na račun 205-185654-03, Komercijalna banka. Za sve dodatne informacije kontaktirati Uredništvo.

SANAMED

ISSN-1452-662X

Publisher

Association of medical doctors “Sanamed”, Novi Pazar

ISSUED THREE TIMES A YEAR

Editorial address

“SANAMED”, St. Palih boraca 52, 36300 Novi Pazar, Serbia
email: sanamednp@gmail.com, www.sanamed.rs

Print

“OFSET”, Kraljevo

Circulation

500

Subscription

Annual subscriptions: 4500 RSD for domestic institutions and 1500 RSD for individuals. For readers abroad, annual subscription is 75 Euro (in Dinar equivalent at the exchange rate on the day of payment). For further instructions and informations, contact Editorial Board.

SANAMED

Number 14(2)/2019

CONTENTS

SANAMED

Number 14(2)/2019

SADRŽAJ

Čitaj da shvatiš

Piši da preneseš

Uradi da te pamte

* * *

Read to understand

Write to impart

Work to be remembered

Avdo Ćeranić

SANAMED
2019; 14(2): 131–145
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i2.336
UDK: 615.099:546.57
ID: 278333452
Original article

THE PROTECTIVE ROLE OF TANNIC ACID AGAINST POSSIBLE HEPATO-NEPHROTOXICITY INDUCED BY SILVER NANOPARTICLES ON MALE RATS

Mosa F Israa,[1*] Youssef Mokhtar,[2] Shalaby Thanaa,[3] Mosa F Osama[4]

[1*] Department of Environmental Studies, Institute of Graduate Studies and Research, Alexandria University, Alexandria, Egypt
[2] Department of Environmental Studies, Institute of Graduate Studies and Research, Alexandria University, Alexandria, Egypt
[3] Department of Biophysics, Medical Research Institute, Alexandria University Alexandria, Egypt
[4] Department of Public Health, Health Sciences College at Leith, Umm Al Qura University, Al-Leith, Makkah, Saudi Arabia

Primljen/Received 22. 05. 2019. god.
Prihvaćen/Accepted 25. 07. 2019. god.

Abstract: Silver nanoparticles (AgNPs) are being used extensively for biomedical purposes regarding to their broad antimicrobial activity, however their toxicity has been addressed in only few studies. In the present study, we aimed to prepare and characterize AgNPs, investigate their adverse effect on liver and kidney functions, and also elucidate the hepato-nephro protective ability of tannic acid in male rats. The obtained results showed that AgNPs caused oxidative stress throughout the induction of thiobarbituric acid-reactive substances (TBARS) and the reduction of the activities of antioxidant enzymes (GST, SOD, CAT, GPx) and the levels of glutathione. Hepatic markers enzymes (AST, ALT, ALP, ACP, LDH and GGT), total bilirubin, urea, creatinine and lipid profile were increased, while hematological parameters were decreased. Histopathological investigations indicated marked degeneration of hepatocytes, endothelial cells of renal which with its role has confirmed the hepatotoxicity and nephrotoxicity induced by AgNPs. The presence of tannic acid along with AgNPs showed obvious improvements in the injured liver and kidney tissues. The protective effect of tannic acid against the toxicity of AgNPs might be due to its antioxidant properties and scavenging abilities against active free radicals.

Key words: Silver nanoparticles, Tannic acid, nanotoxicology, Hepatotoxicity, renal damage, Reactive oxygen species, DNA oxidation, oxidative stress, histopathological architecture.

INTRODUCTION

During the last decade, a rising research has been done on metal nanoparticulates due to their excellent catalytic, optical, electrical, magnetic, antimicrobial and other physical and chemical characteristics; those are completely different from their bulk size. Silver nanoparticles (AgNPs) are believed to be one of the most substantial types of metal nano-materials which have been used increasingly in medical field, because of their strong bacteriostatic (1), antiviral (2) and fungicidal effects (3). AgNPs are widely used in dietary supplementations, for dental hygiene, wound dressing and also in medical devices and implants (4). Moreover, silver nanoparticles have been used in a wide range in consumer products especially air and water filters due to their antiseptic properties, towels, clothes, paints and cleansers for surface cleansing, as well as many applications in biotechnology and life sciences (5). They have also been used for the treatment of many diseases such as breast cancer, leukemia and different carcinomas (6). Regular consumption and direct contact with products like medications and food containing silver nanoparticles represent a sustainable source of AgNPs which when emitted to the environment might produce a substantial contamination hazard (7) and a prospective risk to human health (8).

Silver nanoparticles antibacterial properties influenced in many applications in several areas such as food, health and electronics. Its increased usage contri-

butes to its consumer exposure which with its role rise a variety of questions in terms of safety risk. However, AgNPs effects on humans is still under inspection. In the literature, most studies on AgNPs are *in vitro*, intravenous, inhalation, intraperitoneally and subcutaneous (9). It has been elucidated that AgNPs induced cytotoxicity *in vitro* though free radical generation (10).

Silver Nanoparticles can be taken in the gastrointestinal (GI) barrier, enter the circulation system, and translocation in different organs i.e. (Liver, brain, kidney, lung, spleen and small intestine) (11). The mechanism of toxicity of silver nanoparticles is related to reactive oxygen species (ROS) generation and oxidative stress elevation resulting in lipid peroxidation, apoptosis, damage to protein and DNA, membrane leakage and kidney dysfunction (12). AgNPs release silver ions in suspension, because of its surface charge, particle size or coating (11). Moreover, ions released from silver nanoparticles could penetrate cells and spread through biological barriers to achieve equilibrium concentration (13).

Reactive oxygen species cause numerous toxic effects which are associated with various pathogens, including neurodegeneration, carcinogenesis, atherosclerosis, aging and diabetes. However, it is well known that protracted exposure to ROS in high concentrations leads to several disorders (14, 15). Therefore, an increasing requirement for antioxidants has been made in order to identify natural sources for vigorous antioxidant polyphenols and phytochemicals. Tannic acid is a hydrolysable natural polyphenol that has been extensively found in a range of plants such as grapes, oak, and green tea (16). It has been approved safe for direct usage in pharmaceutical products by the FDA (17). Tannic acid has been used as a medication for the treatment of vasodilation, intestinal lesions and reducing inflammation because of its antimicrobial activity (18), inhibition of apoptosis of tumor cells with antigenic and antimutagenic activity (19), decreasing pain (20), and hypoglycemic effects regulation (21). Phenolic acid antioxidant activity is due to several different mechanisms, such as scavenging free-radical, donating hydrogen atoms, quenching singlet oxygen, chelating metal ion, activating antioxidant enzymes and acting as radical'ssubstrate such as hydroxyl or superoxide. The main defense mechanism of phenolic acid is torevoke ROS generation and thus avoid oxidative damage formation (15).

Given the potential oxidative effects of AgNPs, we aimed at the present study to investigate the possible toxic effect of AgNPs following 77 days repeated i.p. exposure on some biomarkers of oxidative stress, histopathological alterations, biochemical and hematological parameters in rat's liver and kidney. Also, study the mitigation effect of tannic acid against AgNPs-induced toxicity.

MATERIAL AND METHODS

Chemicals

Silver nitrate ($AgNo_3$), trisodium citrate dehydrates ($C_6H_5O7Na_3.2H_2O$, 99.99%) and tannic acid ($H_{76}C_{52}O_{46}$, MW 1701.20) were purchased from Sigma Aldrich (St. Louis, MO, USA). All other chemicals used in the experiment were of analytical grade or highest grade available.

Synthesis of silver nanoparticles

Silver nanoparticles were prepared by chemical reduction method according to Fang et al. (22), by aqueous $AgNO_3$ reducing with sodium citrate at boiling temperature. In typical procedure, a 50 ml of 1 mM $AgNO_3$ was heated till boiling. To this solution, 5 ml of 1% $Na_3C_6H_5O_7$ was added drop by drop. The solution was heated at boiling point under continuous stirring. The reaction was allowed to take place until the color changed to greenish yellow. The solution was then cooled to room temperature.

Characterization of silver nanoparticles

Nanoparticles size and morphology were analyzed with a transmission electron microscope (TEM; JEOL JSM 100CX, Japan), a drop of synthesized silver nanoparticles solution was placed on the carbon coated copper (C/Cu) grids and kept overnight under vacuum desiccation. The carbon coated copper grids were then loaded onto a specimen holder. TEM micrographs of the sample were taken by TEM operated at 80kV accelerating voltage. Silver colloids optical absorption features in the UV-visible range of 300-700 nm wave length were measured using UV-VIS Spectrophotometer (Jenway 6405, UK). The samples for X-ray diffraction (XRD) analysis were made to study the crystalline nature of the prepared AgNPs by (Shimadzu, XRD-7000, Maxima, Japan) operated at 30 kV and30 mA current with CuKα radiation and scan between 10 to 79.9° (2θ) with 0.2° step intervals

The particle size of silver nanoparticle was calculated from the width of the XRD peaks, using the Debye-Scherrer formula:

$D = 0.94\ \lambda / â\ Cos\ è\theta$

Where D is the average crystallite domain size perpendicular to the reflecting planes, λ is the wavelength of X-ray, βâ is the angular full width at half maximum (FWHM), and θ is the angle of diffraction (Bragg's angle).

FT-IR spectrum was obtained using FT-IR spectrophotometer (Shimazdu IR Prestige-21). The sample was mixed uniformly with potassium bromide at 1:100 (sample: KBr) ratio respectively and incubated at 110 °C overnight. After that, the mixture was cooled down in desiccators. The KBr discs were prepared by compressing the powders (mixture of sample and KBr) in a hydraulic press. The discs were scanned in the range of 400–4000 cm^{-1} to obtain FT-IR spectrum.

Test chemicals and treatment

Silver nanoparticles were suspended directly in deionized water and dispersed by ultrasonic vibration. The size of AgNPs (less than 100 nm) was tested at a dose of 50 mg/kg BW/day and was injected intraperitoneally (IP) every day for 77 consecutive days to male Wistar rats, this dose was chosen according to Sharmaet al. (23). On the other hand, the dose of tannic acid (100 mg/kg BW/day) was given orally for the same period of time and was chosen according to Di Meo et al. (14).

Animals and experimental design

This experiment followed the ethics criterion of the Animal Ethics Committee of the Institute of Graduate Studies and Research, Ethical Approval No.AP-GI-07/2015. Alexandria University (Alexandria, Egypt). The study was done on 40 adults male Wistar rats weighing (200 ± 22) g obtained from the Faculty of Medicine, Alexandria University, Egypt. Animals were housed in a comfortable environment kept on basal diet and tap water which were provided ad libitum. Animals were maintained in a controlled atmosphere, a temperature of 25 ± 5 °C and 50-70% humidity. They were monitored during the period of treatment. Food and water intake, and body weights were weekly recorded through the whole experimental period. After acclimation for 2 weeks; they were randomly divided into 4 equal groups and each cage housed a maximum of 5 rats. The first group was used as control; the second group was orally treated with tannic acid (100 mg/kg BW/day). The third group was intraperitoneally (IP)treated with silver nanoparticles (50 mg/kg BW/day) and the forth group was treated with both silver nanoparticles and tannic acid. Rats were administered their respective doses of silver nanoparticles and tannic acid every day for 77 consecutive days.

Blood samples collection and tissue preparations

At the end of the 77th day of the experimental period, animals were anaesthetized with diethyl ether and blood samples were rapidly taken from the rats' aorta after scarification then collected in test tubes containing heparin and placed on ice immediately. The collected blood was centrifuged at 860 xg for 20 min for the separation of plasma. The plasma was kept at - 80 °C until tested parameters analyses. Liver and kidney were removed, washed using saline solution and adhering fat and connective tissues were removed. Liver and kidney were minced and homogenized separately (10%, w/v), in ice-cold sucrose buffer (0.25 M) in a Potter–Elvehjemhomogenizer. Homogenates were then centrifuged at 10,000 xg for 20 min at 4 °C, in order to pellet the cell debris and collect the supernatant, then stored at – 80 °C for the tested parameters determination.

Markers of oxidative stress and antioxidant parameters

Lipid peroxidation index in kidney and liver homogenate was assayed as thiobarbituric acid-reactive substances (TBARS) which were measured at 532 nm, using 2-thiobarbituric acid (2,6-dihydroxypyrimidine-2-thiol; TBA). TBARS levels were measured by the method of Tappel&Zalkin (25). The activity of superoxide dismutase (SOD) was measured according to Mishra &Fridovich (26). The assay procedure of SOD determination involves epinephrine inhibition of auto-oxidation in an alkaline medium (pH 10.2) to adrenochrome, which is inhibited by the presence of SOD. Epinephrine was added to the assay mixture, containing tissue supernatant and the change in coefficient extinction was followed at 480 nm in a Spectrophotometer. The glutathione peroxidase (GPx) activity was assayed by the method of Chiu et al. (27) in kidney and liver homogenate. The activity of Glutathione S-transferase (GST) was determined according to Habig et al. (28). The GST activity was measured in kidney and liver homogenate and p-nitrobenzyl chloride was used as substrate. The measure absorbance was detected at 310 nm using UV-Double Beam Spectrophotometer. The activity of catalase (CAT) was determined using the Luck method involving the hydrogen peroxide decomposition (29). The CAT activity was measured at 240 nm by calculation the rate of hydrogen peroxide degradation. The content of reduced glutathione (GSH) was determined and the method applied metaphosphoric acid for precipitation of protein and DTNB for color development and its density was measured at 412 nm. GSH content was determined according to the method of Jollow et al. (30).

Biochemical and hematological parameters

Plasma total protein, albumin, urea, creatinine, and total bilirubin were measured with kits from Biosystems S.A (Costa Brava 30, Barcelona, Spain). The

activities of plasma and liver aspartate transaminase, alanine transaminase, alkaline phosphatase, acid phosphatase, lactate dehydrogenase and gamma glutamyte transaminase (GGT) were measured with kits from Biosystems S.A (Costa Brava 30, Barcelona, Spain). **HA-VET CLINDIAG** was used to measure the following hematological parameters: Red Blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cells and platelets counts.

Histological section preparation of liver and kidney

Liver and kidney specimens obtained from rats were immediately fixed in 10% formalin, and treated with plain grade of alcohol and xylol, embedded in paraffin and sectioned at 4-6 μm thickness. The sections were stained with (H&E) for studying the histopathological changes Drury et al. (31).

Statistical analysis

The results were reported as means ± SE, and statistical analysis for the previously studies parameters were performed following the general linear model (GLM) produced by SAS Institute (32). Duncan's New Multiple Range Test was used to test the significance of the differences between means [33]. Values of $p < 0.05$ were supposed to be statistically significant.

RESULTS

Preparation and characterization of silver nanoparticles

UV-Vis spectroscopy is a method used to examine nanoparticles production based on their optical characteristic. Silver nanoparticles absorption band shows strong absorption at 425 nm (Figure 1). The typical Transmission Electron Microscopy (TEM) images of the synthesized AgNPs are presented in Figure 2 (A and B). It is observed that most of them were spherical in shape and homogeneously distributed (Figure 2 (A and B)). The Scanning Electron Microscopy (SEM) image of silver nanoparticles is shown in Figure 3. The morphology of AgNPs shown in Figure 4 confirms that AgNPs are spherical in shape in the range of 17-51nm.

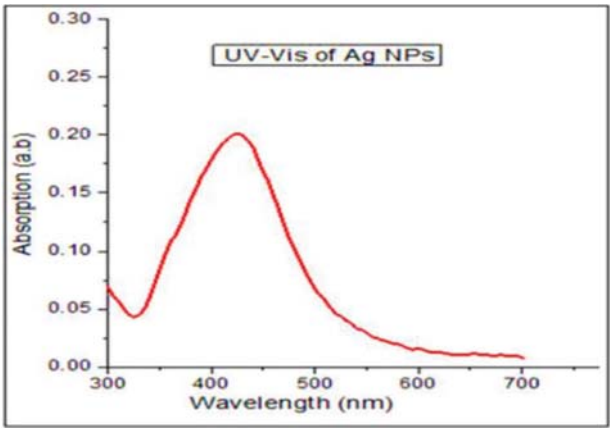


Figure 1: *UV-Vis absorption spectrum of silver nanoparticles (AgNPs)*

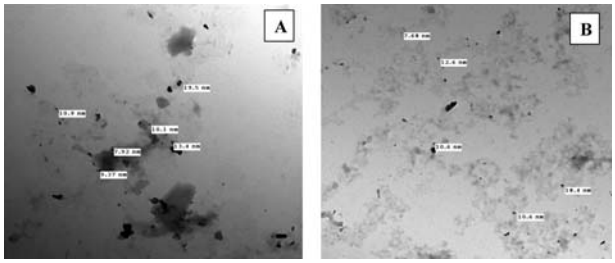


Figure 2: *Transmission Electron Microscopy (TEM) image of AgNPs (A&B)*

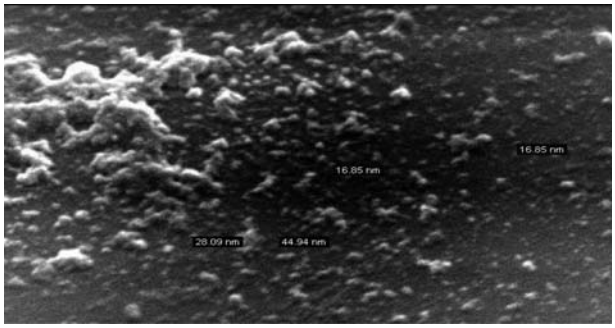


Figure 3: *Scanning Electron Microscopy (SEM) of AgNPs*

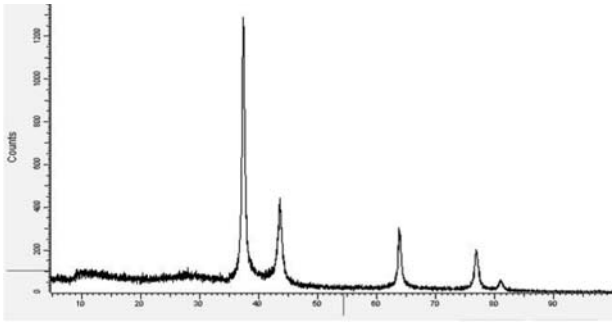


Figure 4: *XRD pattern of silver nanoparticles*

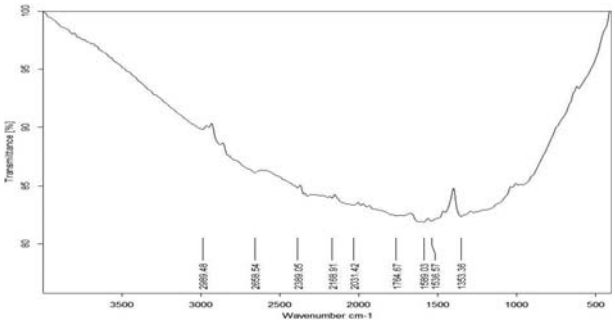


Figure 5: *FTIR spectra of AgNPs*

The peaks at 2θ = 38.07°, 44.18°, 64.37° and 77.29° can be assigned to reflections from the 1 1 1, 2 0 0, 2 2 0 and 3 1 1 planes respectively, of metallic silver in FCC phase. Figure 5 shows various peaks for the FT-IR spectrum recorded for AgNPs. The peak at 1599 cm^{-1} is very broad and strong, and can be assigned to the hydroxyl group, also a prominent and very sharp peak is observed at 1353 cm^{-1} due to the nitrate ions group.

Markers of oxidative stress and antioxidant parameters

The levels of thiobarbituric acid-reactive substances (TBARS) and reduced glutathione (GSH), and the activities of superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione S-transferase (GST) and catalase (CAT) were measured in liver and kidney of male rats treated daily for 77 days with tannic acid, AgNPs and their combination were presented in Table 1 and 2 and Figure 6 and 7. Data indicated that treatment with AgNPs alone significantly ($P < 0.05$) decreased the activities of SOD, CAT, GST, GPx and the level of GSH, and increased the levels of TBARS in liver and kidney compared to control group. While, treatment with tannic acid alone significantly ($P < 0.05$) increased the activities of SOD, CAT, GST, GPx and the levels of GSH, but decreased TBARS levels in liver and kidney. While, the presence of tannic acid along with AgNPs in the combination group minimized the toxic effect on all above parameters compared to AgNPs treated group.

Biochemical parameters

Table 3 and Figure 8 represented the mean values of the activities of alanine transaminase (ALT), aspartate transaminase (AST), acid phosphatase (ACP), alkaline phosphatase (ALP), gama-glutamyl transferase (GGT) and lactate dehydrogenase (LDH) in plasma and liver of male rats treated with tannic acid, AgNPs,

Table 1. *Liver levels of thiobarbituric acid-reactive substances, glutathione, superoxide dismutase, glutathione peroxidase, glutathione S-transferase and catalase of male rats treated with tannic acid, silver nanoparticles (AgNPs)and their combination*

Parameter	Experimental groups			
	Control	Tannic Acid	AgNPs	AgNPs+TA
TBARS (mg/ml protein)	21.8 ± 1.40^{c}	16.0 ± 1.67^{d}	43.8 ± 2.59^{a}	36.0 ± 1.55^{b}
GSH (mU/mg protein)	4.83 ± 0.20^{b}	5.88 ± 0.09^{a}	3.21 ± 0.19^{d}	3.92 ± 0.11^{c}
SOD (mU/mg protein)	5.74 ± 0.25^{b}	6.70 ± 0.17^{a}	4.19 ± 0.21^{d}	4.84 ± 0.13^{c}
GPx (mU/mg protein)	34.8 ± 1.31^{b}	47.3 ± 2.00^{a}	27.6 ± 1.19^{d}	32.3 ± 1.50^{bc}
GST (mU/mg protein)	1.28 ± 0.03^{b}	1.57 ± 0.05^{a}	0.86 ± 0.05^{d}	1.09 ± 0.03^{c}
CAT (mU/mg protein)	59.17 ± 2.36^{b}	70.65 ± 2.25^{a}	38.27 ± 1.54^{d}	47.81 ± 2.40^{c}

* Mean values within a column not sharing a common superscript letter (a, b, c) were significantly different, $p < 0.05$.
* TBARS = Thiobarbituric acid-reactivesubstances,GSH = Reduced glutathione concentration, SOD = Superoxide dismutase, GPx = Glutathione peroxidase, GST = Glutathione S-transferase, CAT = Catalase.

Table 2. *Kidneylevels of thiobarbituric acid-reactive substances, glutathione, superoxide dismutase, glutathione peroxidase, glutathione S-transferase and catalase of male rats treated with tannic acid, silver nanoparticles (AgNPs)and their combination*

Parameter	Experimental groups			
	Control	Tannic Acid	AgNPs	AgNPs+TA
TBARS (mg/ml protein)	27.67 ± 1.36^{c}	22.17 ± 1.92^{d}	43.83 ± 1.99^{a}	36.00 ± 1.79^{b}
GSH (mU/mg protein)	5.41 ± 0.33^{b}	6.00 ± 0.37^{a}	3.77 ± 0.17^{d}	4.63 ± 0.12^{c}
SOD (mU/mg protein)	6.93 ± 0.30^{b}	8.02 ± 0.19^{a}	3.61 ± 0.20^{d}	5.46 ± 0.28^{c}
GPx (mU/mg protein)	58.01 ± 2.43^{b}	68.49 ± 2.95^{a}	27.07 ± 1.34^{d}	40.50 ± 0.67^{c}
GST (mU/mg protein)	1.41 ± 0.06^{b}	1.73 ± 0.06^{a}	0.92 ± 0.04^{d}	1.24 ± 0.07^{c}
CAT (mU/mg protein)	57.02 ± 2.22^{b}	71.26 ± 1.97^{a}	31.12 ± 1.71^{d}	47.23 ± 1.85^{c}

* Mean values within a column not sharing a common superscript letter (a, b, c) were significantly different, $p < 0.05$.
* TBARS = Thiobarbituric acid-reactivesubstances, GSH = Reduced glutathione concentration, SOD = Superoxide dismutase, GPx = Glutathione peroxidase, GST = Glutathione S-transferase, CAT = Catalase.

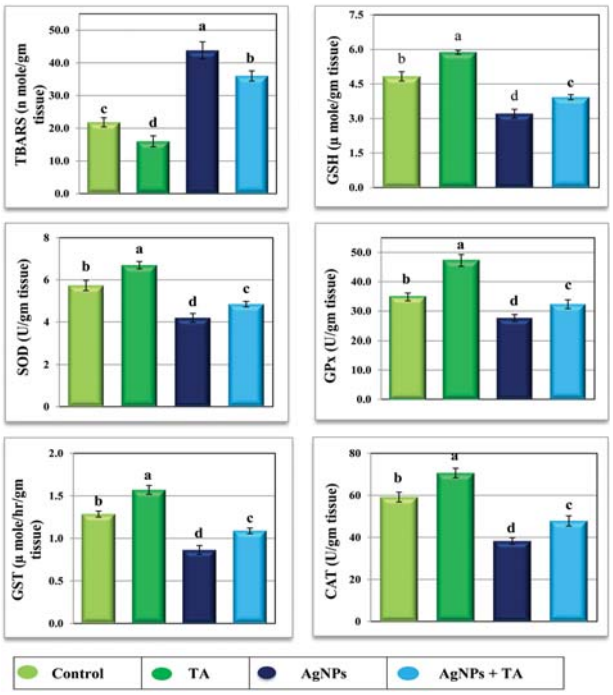


Figure 6: *Mean values ± SE of liver thiobarbituric acid-reactive substances (TBARS; n mole/gm tissue), reduced glutathione (GSH; µ mole/gm tissue), superoxide dismutase (SOD; U/gm tissue), glutathione peroxidase (GPx; U/gm tissue), and glutathione S-transferase (GST; µ mole/hr/gm tissue), catalase (CAT; U/gm tissue)*

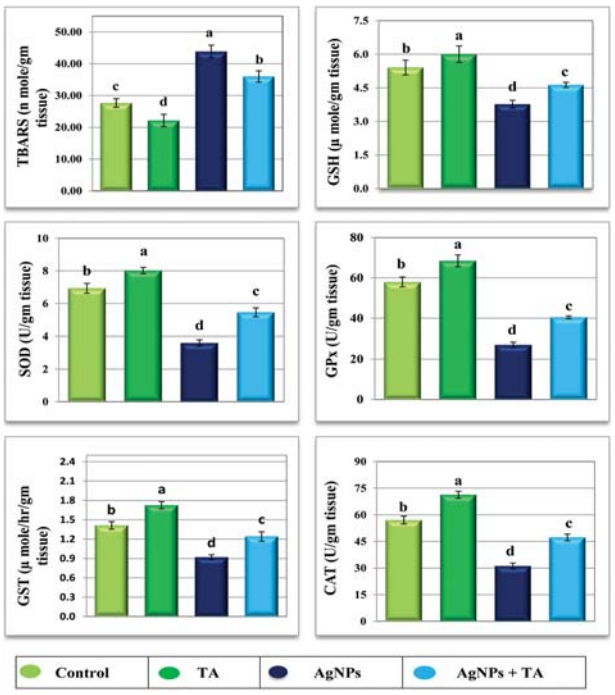


Figure 7: *Mean values ± SE of kidney thiobarbituric acid-reactive substances (TBARS; n mole/gm tissue), reduced glutathione (GSH; µ mole/gm tissue), superoxide dismutase (SOD; U/gm tissue), glutathione peroxidase (GPx; U/gm tissue), glutathione S-transferase (GST; µ mole/hr/gm tissue), catalase (CAT; U/gm tissue)*

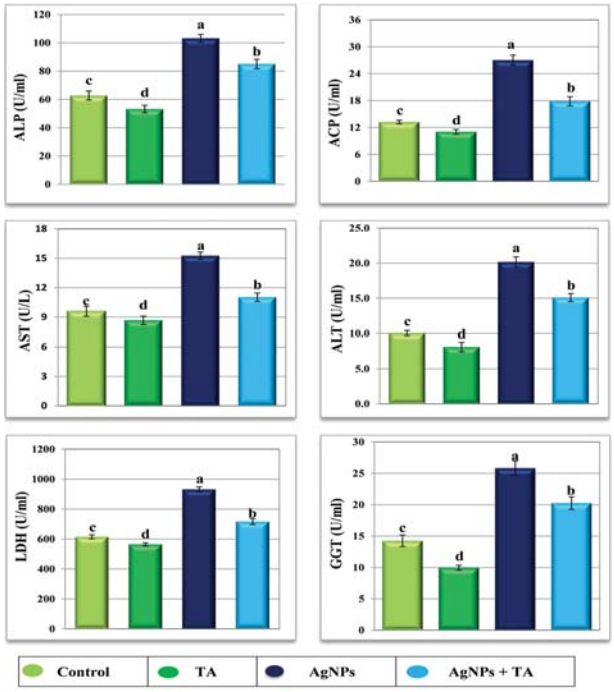


Figure 8: *Mean values ± SE of plasma alkaline phosphatase (ALP; U/ml), acid phosphatase (ACP; U/ml), aspartate transaminase (AST; U/L), alanine transaminase (ALT; U/ml), plasma lactate dehydrogenase (LDH; U/ml), gamaglutamyle transaminase (GGT; U/ml) of male rats treated with tannic acid, silver nanoparticle and their combination*

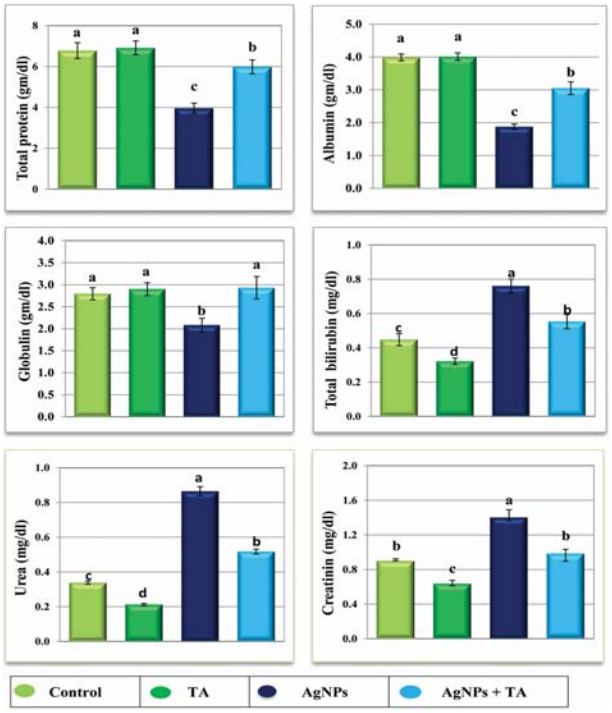


Figure 9: *Mean values ± SE of plasma total protein (gm/dl), albumin (gm/dl), globulin (gm/dl), Total bilirubin (mg/dl), urea (mg/dl) and creatinine (mg/dl) of male rats treated with tannic acid, silver nanoparticles and their combination*

and their combination for 77 days. Results showed that treatment with AgNPs significantly ($P < 0.05$) increaseed plasma ALP, ACP, LDH and GGT activities compared to control group. On the other hand, treatment with tannic acid alone caused significant ($P < 0.05$) decrease in the activities of these enzymes compared to control group. The combination group showed significant decrease in the activities of studied enzymes compared to AgNPs treated grup.

The mean values of plasma total protein, albumin, globulin, total bilirubin, urea and creatinine after 77 days experimental period was shown in Table 4 and Figure 9. Treatment with AgNPs alone resulted in a significant ($P < 0.05$) decrease in total protein, albumin and globulin, and a significant ($P < 0.05$) increase in plasma total bilirubin, urea, and creatinine compared to control group. While, treatment with tannic acid alone showed non-significant increase in plasma levels of to-

Table 3. *Plasma enzyme activities of male rats treated with tannic acid, silver nanoparticles (AgNPs) and their combination*

Parameter	Experimental groups			
	Control	**Tannic acid**	**AgNPs**	**AgNPs + Tannic acid**
ALP (U/L)	62.80 ± 3.16^{c}	53.23 ± 2.64^{d}	103.18 ± 2.78^{a}	85.08 ± 3.29^{b}
ACP (U/L)	13.23 ± 0.41^{c}	11.05 ± 0.53^{d}	27.03 ± 1.13^{a}	17.85 ± 1.02^{b}
AST(U/L)	9.58 ± 0.50^{c}	8.67 ± 0.41^{d}	15.28 ± 0.37^{a}	11.03 ± 0.43^{b}
ALT(U/L)	10.04 ± 0.42^{c}	8.11 ± 0.76^{d}	20.18 ± 0.83^{a}	15.08 ± 0.67^{b}
LDH (U/L)	615.0 ± 5.78^{c}	564.3 ± 8.85^{d}	931.7 ± 16.94^{a}	715.8 ± 8.33^{b}
GGT (U/L)	14.25 ± 0.91^{c}	9.94 ± 0.41^{d}	25.85 ± 1.13^{a}	20.25 ± 1.00^{b}

* Mean values within a column not sharing a common superscript letter (a, b, c) were significantly different, $p < 0.05$.
*ALP = Alkaline phosphatase, ACP = Acid phosphatase, AST = Aspartate transaminase, ALT = Alanine transaminase, LDH = Lactate dehydrogenase, GGT = Gamaglutamyle transaminase.

Table 4. *Plasma total protein, albumin, globulin, total bilirubin, urea and creatinine of male rats treated with Tannic acid, silver nanoparticles (AgNPs) and their combination*

Parameter	Experimental groups			
	Control	**Tannic acid**	**AgNPs**	**AgNPs + Tannic acid**
Total protein (g/dl)	6.78 ± 0.38^{a}	6.91 ± 0.34^{a}	3.96 ± 0.25^{c}	5.98 ± 0.34^{b}
Albumin (g/dl)	3.99 ± 0.10^{a}	4.01 ± 0.12^{a}	1.88 ± 0.08^{c}	3.05 ± 0.19^{b}
Globulin (g/dl)	2.79 ± 0.14^{a}	2.80 ± 0.14^{a}	2.08 ± 0.16^{b}	2.93 ± 0.26^{a}
Total bilirubin (mg/dl)	0.45 ± 0.04^{c}	0.32 ± 0.02^{d}	0.76 ± 0.04^{a}	0.55 ± 0.04^{b}
Urea (mg/dl)	0.34 ± 0.1^{c}	0.21 ± 0.01^{d}	0.87 ± 0.03^{a}	0.52 ± 0.02^{b}
Creatinine (mg/dl)	0.90 ± 0.03^{b}	0.64 ± 0.04^{c}	1.40 ± 0.10^{a}	0.98 ± 0.06^{b}

* Mean values within a column not sharing a common superscript letter (a, b, c) were significantly different, $p < 0.05$.

Table 5. *Hematological parameters of male rats treated with Tannic acid, silver nanoparticles (AgNPs) and their combination*

Parameter	Experimental groups			
	Control	**Tannic acid**	**AgNPs**	**AgNPs + Tannic acid**
RBC (10^{6}/ml)	6.27 ± 0.52^{b}	7.07 ± 0.43^{a}	4.19 ± 0.10^{d}	5.31 ± 0.22^{c}
HGB (g/dl)	21.48 ± 1.23^{b}	23.91 ± 1.17^{a}	16.53 ± 0.91^{d}	18.64 ± 0.53^{c}
HCT (%)	32.58 ± 1.25^{b}	36.73 ± 1.60^{a}	24.60 ± 1.85^{d}	27.90 ± 1.45^{c}
MCV (fl)	55.50 ± 3.13^{b}	62.67 ± 1.76^{a}	41.33 ± 1.33^{d}	49.83 ± 1.45^{c}
MCH (pg)	35.15 ± 2.21^{b}	39.75 ± 1.72^{a}	25.90 ± 1.50^{d}	30.67 ± 1.61^{c}
MCHC (pg)	71.42 ± 2.09^{b}	80.17 ± 2.44^{a}	55.73 ± 1.91^{d}	61.25 ± 2.23^{c}
PLT (10^{3}/ ml)	183.67 ± 5.4^{b}	207.3 ± 9.35^{a}	66.17 ± 4.13^{d}	112.17 ± 3.26^{c}
WBC (10^{3}/ ml)	11.4 ± 0.52^{cd}	12.7 ± 0.43^{c}	17.0 ± 0.10^{a}	14.4 ± 0.22^{b}

* Mean values within a column not sharing a common superscript letter (a, b, c) were significantly different, $p < 0.05$.
*RBC= red blood cells, HGB= hemoglobin, HCT= hematocrit value, MCV= mean corpuscular volume, MCH= mean corpuscular hemoglobin, MCHC= mean corpuscular hemoglobin concentration, PLT= platelets (10^{3}/ ml) and WBC= white blood cells(10^{3}/ ml).

tal protein, albumin and globulin, and non-significant ($P < 0.05$) decrease in plasma total bilirubin, urea and creatinine compared to the control group. On the other hand, the presence of tannic acid with AgNPs in the combination group increased the concentration of plasma total protein, albumin and globulin, and decreased plasma total bilirubin, urea and creatinine. But these values did not reach the values of control group.

Hematological parameters

Table 5 and Figure 10 represented the mean values of the hematological parameters (white blood cells; WBCs, red blood cells; RBC, hemoglobin; HGB, hematocrit value; HCT, mean corpuscular volume; MCV, mean corpuscular hemoglobin; MCH, mean corpuscular hemoglobin concentration; MCHC, platelets; PLT) of male rats treated with tannic acid, silver nanoparticles, and their combination for 77 days. Results showed that treatment with AgNPs caused significant ($P < 0.05$) increase in WBCs, while caused significant ($P < 0.05$) decrease in RBC, HGB, HCT, MCV, MCH, MCHC and PLT compared to control group. On the other hand, treatment with tannic acid alone caused significant ($P < 0.05$) decrease in WBCs and caused significant ($P < 0.05$) increase in RBC, HGB, HCT, MCV, MCH, MCHC and PLT compared to control. Results showed that the presence of tannic acid along with AgNPs in

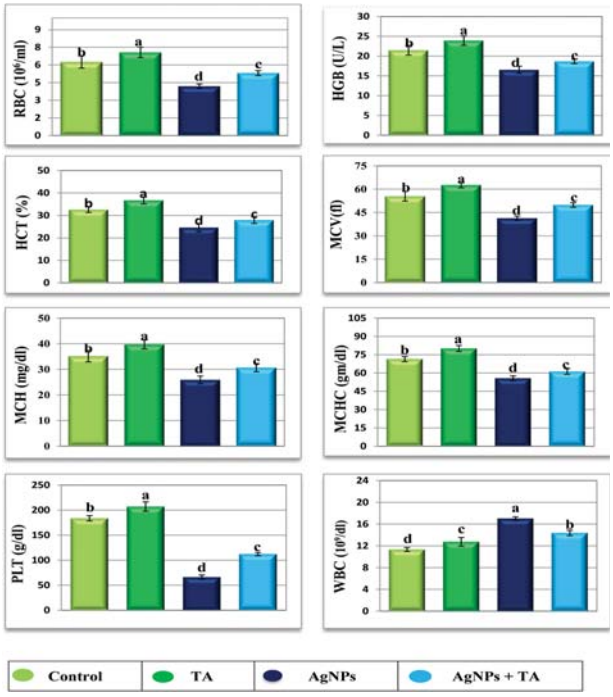


Figure 10: *Mean value ± SE of red blood cells (RBC; 10^6/ml), hemoglobin (HGB; U/L) and hematocrit (HCT; %), mean corpuscular volume (MCV; fl), mean corpuscular hemoglobin (MCH; mg/dl), mean corpuscular hemoglobin concentration (MCHC; gm/dl), platelets (PLT; g/dl) and white blood cells (WBC; 10^9/dl) of male rats treated with tannic acid, silver nanoparticles and their combination*

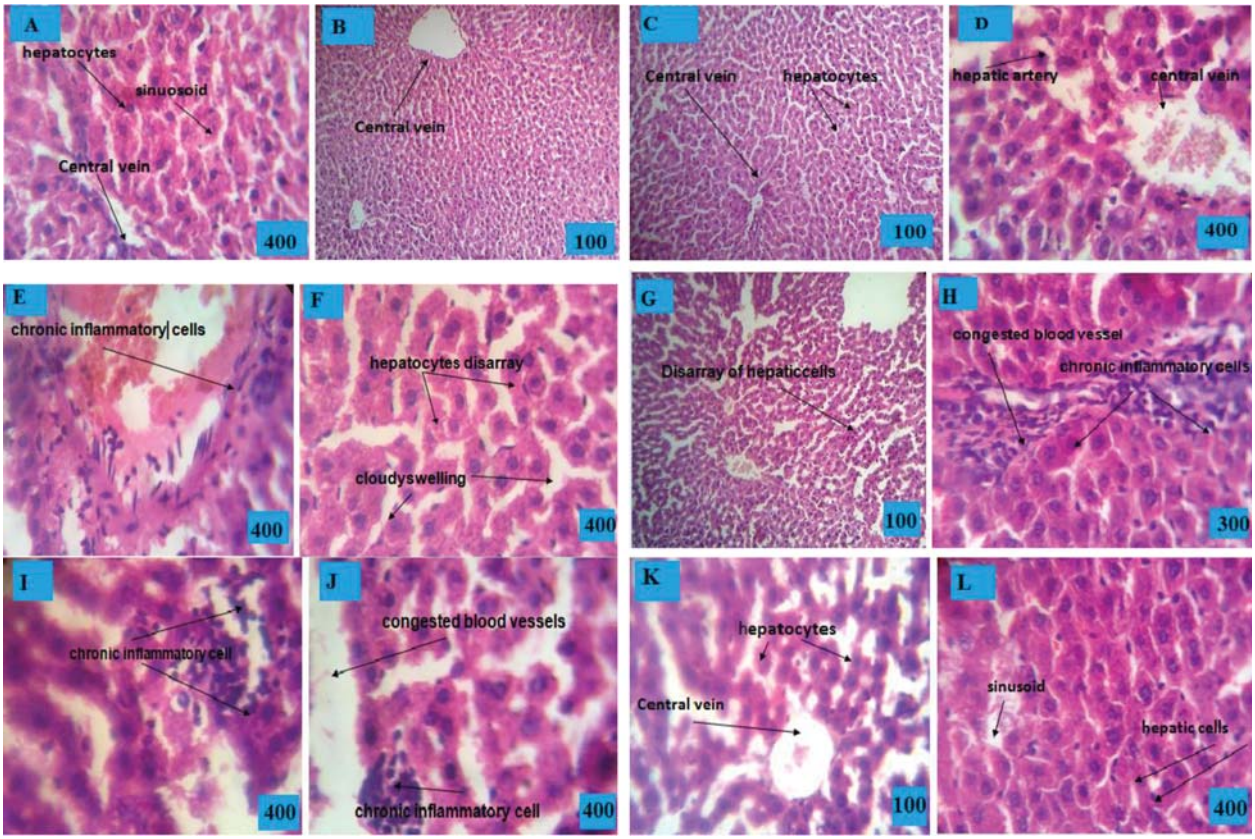


Figure 11: *Photomicrographs of rat liver sections of different experimental groups stained by H&E*

the combination group caused minimization of the toxicity of AgNPs compared to AgNPs treated group.

Histopathological parameters of liver and kidney

Photomicrograph of the liver of control rats (Figure 11 (A and B)) showed normal structure hepatocytes having normal eosinophilic cytoplasm, round nuclei, central vein, portal tracts and blood sinusoids. Photomicrograph of liver of rats treated with tannic acid (Figure 11C) showed also normal structure of hepatocytes having normal eosinophilic cytoplasm, round nuclei central vein, portal tracts and blood sinusoids, while (Figure 11D) showed hepatic lobule, hepatocytes surrounding central vein and normal hepatic artery. Photomicrograph of rats' sliver treated with silver nanoparticles Figure 11(E-J) showed hepatocytes revealed hydropic change, sinusoidal dilatation, Kupffer cell hyperplasia, moderate portal inflammation and piecemeal. Lobular infiltrate by chronic inflammatory cells congested hepatic sinusoids containing red blood cells, with hepatocytes disarray and cloudy swelling is liver hepatocytes (sinusoid). Photomicrograph of liver of rats treated with AgNPs and tannic acid (Figure 11(K and L)) showed improvement of the portal area and a decrease of the inflammation and infiltration of the portal area and hepatocytes.

Photomicrograph of kidney of control rats (Figure 12 (A and B)) showed normal glomeruli and tubules. Also, photomicrograph of rats treated with tannic acid (Figure 12 (C and D)) showed normal glomeruli and tubules in kidney. The tubules are lined by low cuboidal epithelium with eosinophilic cytoplasm. The glomeruli have normal epithelial, endothelial and mesangial cells. Photomicrograph of rats treated with silver nanoparticles showed slightly degeneration and epithelial cell necrosis, in the epithelial lining some of the tubules and mononuclear cell infiltration in the interstitium (Figure 12 (E and F)). Also, treatment with silver nanoparticles showed increase degeneration and renal tubules necrosis in the epithelial lining, some of the tubules and mononuclear cell infiltration in the interstitium, eosinophilic secretion in the tubules lumen and vascularity of glomerular in the Bowman's capsule (Figure 12 (G and H)). While Photomicrograph of rats treated with silver nanoparticles and tannic acid showed improvement of the degeneration and epithelial

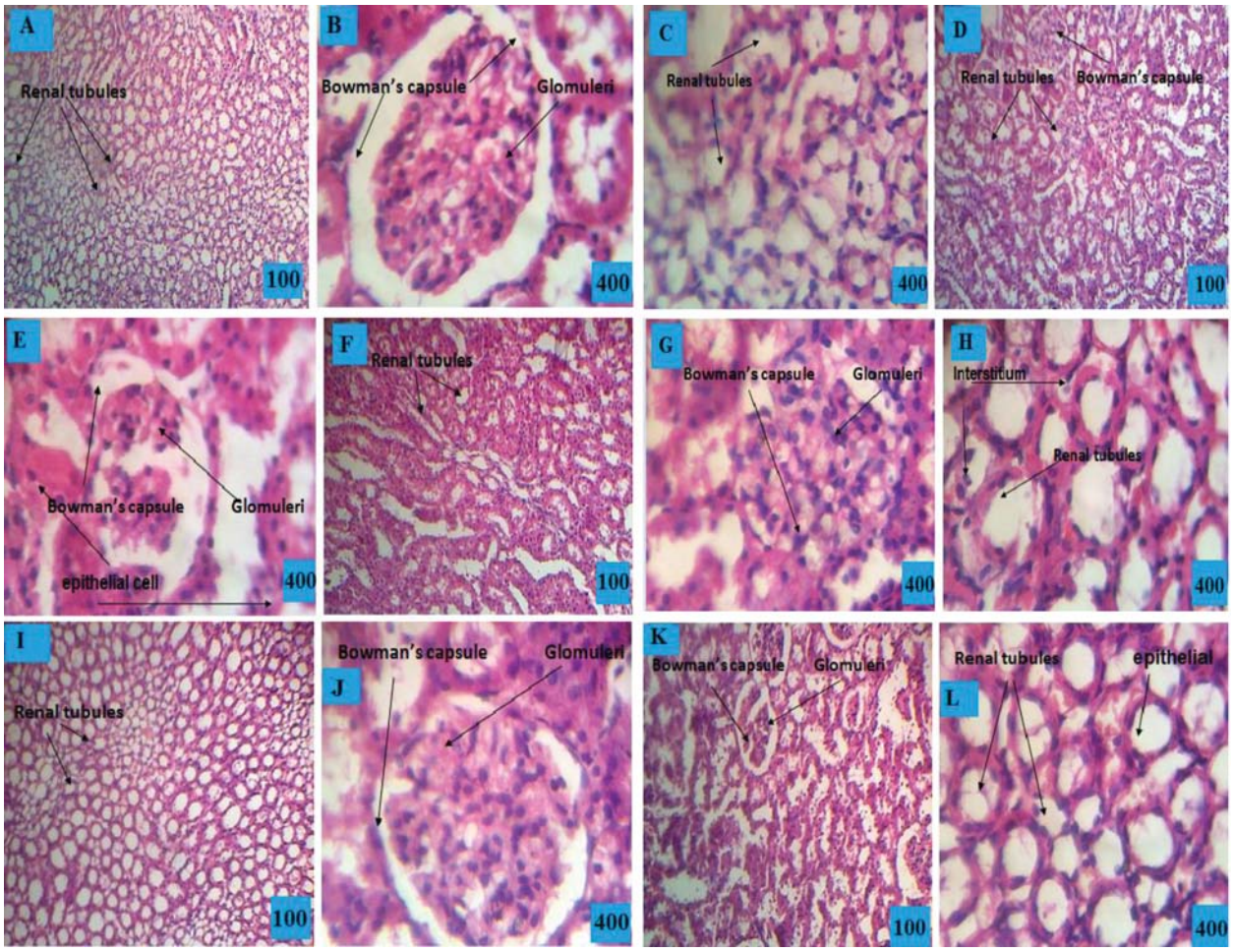


Figure 12: *Photomicrographs of rat kidney sections of different experimental groups stained by H&E*

cell necrosis, in the epithelial lining: some of the tubules and mononuclear cell infiltration in the interstitium and decrease of eosinophilic secretion in the tubules lumen (Figure 12(I-L)).

DISCUSSION

Silver nanoparticles are one of the most commercialized nanoparticles worldwide and its toxicology became an important area of research. As a result of their extremely small size, AgNPs has shown unique chemical and physical characteristics with certain biological effects, which with its role make them attractive in several consumer products. However, these properties also highlight the potential toxicity of AgNPs [34]. Kovvuru et al. (35) and Sarhan & Hussein (36) have investigated the *in vivo* and *in vitro* toxicological effects of AgNPs, showing that with different routes of exposure, certain size and doses, AgNPs could lead to harmful effects in living organisms. Due to AgNPs relative safety as compared to other nanomaterials, short-term studies at low doses have not shown any significant adverse effects of AgNPs. However, there are limited numbers of long-term animal studies, especially on the renal and hepatic system. These studies are required because the release of silver ions by surface oxidation and the nano-crystalline solubility of silver are much higher than metallic silver (37). Silver ions also have strong relationship to sulfhydryl groups of amino acids and proteins causing their precipitation and modifications (38).

Induction of oxidative stress is the major mechanism of toxicity of surrounding nanoparticles (39). By disturbing the balance between antioxidant and oxidant processes, nanoparticles enter the cell and induce intracellular oxidative stress. Extravagant oxidative stress may also modify proteins, lipids and nucleic acids, which stimulates the defense system of antioxidant or even leads to cell apoptosis (40). He et al. (41) demonstrated that with elevated concentrations of AgNPs, epithelial cells morphology can change to become more fusiform and less polyhedral, rounded and shrunken, because AgNPs elevate the levels of oxidative stress by decreasing the levels of GSH and SOD, and increasing lipid peroxidation, which finally leads to apoptosis by increasing DNA fragmentation and caspase-3 activity. Upon AgNPs interaction with proteins membrane, AgNPs and Ag^{+} may trigger lipid peroxidation and increase cell membrane permeation. Cell membrane damage leads to cytoplasmic contents leakage, such as LDH, and eventually ends up with cell necrosis, while rupture of lysosomal membranes releases cathepsins into the cytoplasm, activating lysosome-mediated apoptosis (40). Furthermore, mitochondrial damage impairs electron transfer, inhibits adenosine triphosphate (ATP) synthesis, triggers oxidative stress, and activates mitochondrion-dependent apoptosis (40, 42). In a previous study, AgNPs has been administered intraperitoneally to mice at very high doses (100, 500, 1000 mg/kg BW) leading to multiple genes alterations in brain's mouse, including genes associated with oxidative stress and inflammation (43). Existing toxicokinetic data indicates that liver, which is the principal detoxifying organ maintaining metabolic homeostasis, accumulates high concentrations of AgNPs (44). For metabolizing various toxic compounds, liver possesses one of the active antioxidant defense system in order to preserve antioxidative/oxidative balance (45). Hence, the present study was designed to indicate AgNPs influence on oxidative stress generation and the activity of enzymatic antioxidant systems in liver and kidney tissues of intraperitoneally treated rats for 77 consecutive days.

Under physiological conditions, the efficient action of enzymatic and non-enzymatic antioxidant defense systems has prevented the damage caused by ROS. SOD, CAT and GPx are the enzymes providing the first line defense against hydrogen and superoxide peroxide. Our results indicated that antioxidant enzymes inhibition in liver and kidney of rats exposed to AgNPs is good evident. We observed that exposure of rats to AgNPs caused statistically significant decrease in GST, GPx, SOD and CAT activities, and GSH levels in liver and kidney. Results of Skalska et al. (46) revealed that GSH/GSSG ratio decreased in brain after exposure to both forms of silver (AgNPs/Ag^{+}), although no change in the level of total glutathione (tGSH) was observed. This reflects increased rates of GSH oxidation to glutathione disulfide (GSSG) as an effect of increased S-thiolation of critical protein thiols and/or direct ROS scavenging.

Liver has been reported as one of the target organs and a predominant site of accumulation of nanoparticles (47). A previous study has demonstrated that AgNPs administration to rats caused significant alterations to the ALP levels (48). Also, Garcia et al. (34) found signiWcant increase of AgNPs levels in liver and signiWcant alterations in enzymatic liver markers. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are a cytoplasmic in location and only largely released into circulation after hepatocyte structural integrity damage; thus, their activities are most commonly used as reliable markers for clinical monitoring of liver function or liver injury (49). Here, the activities of alkaline phosphatase (ALP), acid phosphatase (ACP), aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), gamaglutamyle transaminase (GGT) increase

in plasma signing a hepatic harmful effect in rats treated with silver nanoparticles. Also, Ebabe Elle et al. (9) found same results in rats exposed to 500 mg/d/kg BW AgNPs for 81 days. The potential of AgNPs to modulate enzyme activity was attributable to their affinity for thiol groups. It is probable that thiol groups in the enzymes made them attractive to AgNPs leading to formation of complexes and consequent modulation of enzyme activity (50).

The decrease in total protein might be due to decreased synthesis, increased loss, increased catabolism, malabsorption or liver disease consequent upon the administration of nanoparticles (51, 52). Braydich-Stolle et al. (53) suggested that plasma albumin concentration may be directly altered, as a result of the loss of albumin through damaged glomeruli in case of renal failure. Consequently, in the present study, the significant decrease in albumin may be evidence on AgNPs-induced nephrotoxicity. Silver nanoparticles increase membrane leakage in mammalian germ line stem cells and increase ROS generation, deplete antioxidant reduced glutathione (GSH) content, and reduce mitochondrial function in rat liver cells. Albendea et al. (54) reported that the depletion in the levels of total protein lead to inhibition of antioxidant enzymes. Proteins are necessary for enzyme synthesis, and any factor blocking the process of protein synthesis will in turn reduce the synthesis of enzymes, including antioxidant enzymes, and consequently lead to the inhibition of these enzymes and this is conformed with the obtained results of liver enzymes. Urea and creatinine are waste products of protein metabolism that need to be excreted by the kidney and increase of these factors is an indication of functional damage to the kidney (55). The level of blood creatinine is proportional to the glomerular filtration rate. Moreover, urea plays an important role in the metabolism of compounds containing protein in animal body (56). Adeyemi and Sulaiman (57) demonstrated that increased red blood cell hemolysis could cause elevated bilirubin beyond the hepatic function capacity. A rise in the level of serum urea may imply impaired renal excretion (58).

Naghsh et al. (59) demonstrated that rats treated with silver nanoparticles, exhibit elevated number of WBC. They justified this phenomenon with the immune response of rats to an external factor causing an increase of the number of white blood cells for phagocytosis of silver nanoparticles. With attention to decrease number of RBC, the falling of RBC can be related to suppressive effect of AgNPs on pluripotent stem cells, producing blood cells, in bone marrow. Lovrić et al. (60) reported that after AgNPs absorption into the GIT, it was capable to enter the blood circulation system, therefore these particles can potentially interact with different metabolites such as: plasma proteins, coagulation factors, platelets, red and white blood cells. For this reason, AgNPs perhaps induce oxidative stress and affect the structure and physiology of the cells adversely, oxidative metabolism, fat membrane structure and function that can destroy red and white blood cells and susceptibly pass reticuloendothelial system of spleen and liver (23). However, no significant effects in hematological parameters were found after 90 days of treatment with different doses of AgNPs (34, 61).

Histopathological changes in liver and kidney of rats treated with AgNPs, which noted in the present study agrees with the obtained data that showed changes in the levels of biochemical parameters in liver and kidney. Arora et al. (62) has found that internalized AgNPs can disrupt the cell membrane integrity, cause lysosomal swelling, and even rupture lysosomal membranes. Tiwari et al. (63) reported that some histopathological changes were observed in kidney of animals treated with AgNPs. Hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS) staining of kidney sections showed damage to basement membrane and brush borders of proximal tubules along with overall decrease in urinary space. TEM analysis indicated significant submicroscopic damage in kidney. Large number of mitochondria were swollen or completely ruptured with total loss of their content. There was pronounced swelling of podocytes with fusion of their foot processes that may affect the glomerular filtration. Such type of submicroscopic changes has been also previously reported in intravenous and subcutaneous treatments (64, 65). These symptoms resemble those observed in 'Minimal change disease' of the kidney, where there are few light microscopic indicators but major changes at the ultramicroscopic level. As reported earlier, this could later lead to development of nephritic syndrome (66) and other chronic diseases of the kidney. TEM analysis also confirmed localization of AgNPs in particle form in the kidney. Also, Tiwari et al. (63) found that kidney sections examination by TEM showed necrotic cellular damage in proximal convoluted tubule (PCT) and distal convoluted tubule (DCT) of animals treated with AgNPs. There was dilation of cellular organelle (mitochondria, endoplasmic reticulum, and Golgi apparatus), damage to plasma membrane, swelling of cells and moderate chromatin condensation which are characteristics of necrotic cell death (67). Tiwari et al. (63) observed significant ROS induced DNA damage in AgNPs treated animals by oxo-8G staining of kidney sections. This was also associated with high levels of ROS and lower GSH/GSSG. Toxic endpoints seen in our study may be cumulative effect of both AgNPsand released ions have been reported previously (63, 68).

Tannic acid is an antioxidant compound, which comprises polyphenolic compound that have been utilized to mitigate various conditions of oxidative stress. Its antioxidant action is believed to originate from its ability to stimulate glutathione (GSH) synthesis, therefore, maintaining intracellular GSH levels (69). Several authors have demonstrated that tannic acid and other polyphenols have antimutagenic and anticarcinogenic activities. Moreover, the consumption of polyphenol-rich fruits, vegetables, and beverages, such as red wine and tea, has been linked with preventive and inhibitory effects in various human cancers and cardiovascular diseases, which may be related at least in part with the antioxidant activity of polyphenols (70). Also, the present data showed that tannic acid decreased the levels of free radicals and increased the activities of antioxidant enzyme therefore minimized the toxic effects of silver nanoparticles. Therefore, the present results showed that tannic acid co-treatment with AgNPs reduced its hepato-renal damage via increasing the activities of antioxidant enzymes in liver and kidney.

CONCLUSION

Finally, we reported that in vivo and intraperitoneally treatment with silver nanoparticles induced deleterious effects on liver and kidney and led to oxidative stress, biochemical and histological changes, and hematotoxicity. Also, our results showed that using tannic acid as antioxidant was capable to alleviate harmful effects of silver nanoparticles on liver and kidney functions to protect healthy tissues and to reduce AgNPs toxicity. Finally, we suggest using tannic acid as a preventive agent along with silver nanoparticles to minimize its hepato-nephrotoxicity.

Abbreviations

GPx — Glutathione peroxidase
GST — Glutathione S-transferase
I.p. — Intraperitoneally
NO — Nitric oxide
GSH/GSSG — Ratio of reduced-to-oxidized glutathione
ROS — Reactive oxygen species
GSH — Reduced glutathione
SOD — Superoxide dismutase
TBARS — Thiobarbituric acid reactive substances
TAC — Total antioxidant capacity
TAG — Triacylglycerol
AgNPs — Silver Nanoparticles
BBB — Blood Brain Barrier
ATP — Adenosine Triphosphate
RNS — Reactive Nitrogen Species
IR — Insulin Receptor
ATPase — Adenosine-triphosphatase
TA — Tannic acid
CAT — Catalase
RBCs — Red Blood Cells
HGB — Hemoglobin
HCT — Hematocrit
MCV — Mean Corpuscular Volume
MCH — Mean Corpuscular Hemoglobin
MCHC — Mean Corpuscular Hemoglobin concentration
WBCs — White Blood Cells
PLT — Platelets
AST — Aspartate Transaminase
ALT — Alanine Transaminase
ALP — Alkaline Phosphatase
ACP — Acid Phosphatase
LDH — Lactate Dehydrogenase
GGT — Gamma glutamyte transaminase
TEM — Transmission Electron Microscope
SEM — Scanning Electron Microscopy
XRD — X-ray Diffractometer
FCC — Face-centered Cubic
FT-IR — Fourier Transform Infrared
LPO — Lipid peroxidation
GR — Glutathione Reductase
GPT — Glutamic pyruvic transaminase
GOT — Glutamic oxaloacetic transaminase
GIT — Gastrointestinal tract

Acknowledgement and Funding

Firstly, I thank Allah the most gracious. This journey would not have been possible without the support of my family, professors and mentors. To my family, thank you for encouraging me in all my pursuits and inspiring me to follow my dreams. I am grateful to my parents, who supported me emotionally and financially. I always knew that they believed in me and wanted the best for me. I heribly acknowledge that this paper has received No funding.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Sažetak

PROTEKTIVNA ULOGA TANINSKE KISELINE U KORELACIJI SA MOGUĆOM HEPATO-NEFROTOKSIČNOŠĆU INDUKOVANOJ NANOČESTICAMA SREBRA KOD MUŽJAKA PACOVA

Mosa F Israa,[1*] Youssef Mokhtar,[2] Shalaby Thanaa,[3] Mosa F Osama[4]

[1*] Department of Environmental Studies, Institute of Graduate Studies and Research, Alexandria University, Alexandria, Egypt
[2] Department of Environmental Studies, Institute of Graduate Studies and Research, Alexandria University, Alexandria, Egypt
[3] Department of Biophysics, Medical Research Institute, Alexandria University Alexandria, Egypt
[4] Department of Public Health, Health Sciences College at Leith, Umm Al Qura University, Al-Leith, Makkah, Saudi Arabia

Nanočestice srebra (AgNPs) se ekstenzivno koriste u biomedicinske svrhe, zbog njihove široke antimikrobne aktivnosti. Međutim njihova toksičnost je opisivana u par studija do sada. Cilj ove studije bio je da se pripreme AgNPs, da se ispitaju neželjeni efekti ovih čestica na hepatične i na bubrežne funkcije, kao i da se bliže objasne hepato-nefrotoksične aktivnosti taninske kiseline kod pacova mužjaka. Dobijeni rezultati su pokazali da AgNPs izazivaju oksidativni stres kroz indukciju reaktivnih supstanci tiobarbitonske aktivnosti (TBARS) i kroz redukciju aktivnosti antioksidantnih enzima (GST, SOD, CAT, GPx) i nivoa glutationa. Vrednosti markera enzimske aktivnosti jetre (AST, ALT, ALP, ACP, LDH i GGT), ukupnog bilirubina, uree, kreatinina i lipidnog profila su bili povećani, dok su vrednosti hematoloških parametara bile snižene. Histopatološka ispitivanja indikovala su značajnu degeneraciju hepatocita, endotelijalnih ćelija bubrega, koje su sa svojom ulogom potvrdile hepatotoksičnost i nefrotoksičnost indukovane AgNPs. Prisustvo taninske kiseline u korelaciji sa AgNPs pokazalo se kao izuzetan napredak kod povrede tkiva jetre i bubrega. Protektivni efekat taninske kiseline u korelaciji sa toksičnošću AgNPs može biti objašnjen antioksidativnim karakteristikama, kao i osobenostima sličnih aktivnosti slobodnih radikala.

Ključne reči: srebrne nanočestice, taninska kiselina, anotoksikologija, hepatotoksičnost, povreda bubrega, reaktivne oksidativne čestice, DNK oksidacija, oksidativni stres, histopatološka arhitektura.

REFERENCES

1. Wu J, Zheng Y, Song W, Luan J, Wen X, Wu Z, et al. In situ synthesis of silver-nanoparticles/bacterial cellulose composites for slow-released antimicrobial wound dressing. Carbohydrate Polymers. 2014; 102: 762-71.

2. Galdiero S, Falanga A, Vitiello M, Cantisani M, Marra V, Galdiero M. Silver nanoparticles as potential antiviral agents. Molecules. 2011; 16(10): 8894-918.

3. Monteiro DR, Silva S, Negri M, Gorup LF, de Camargo ER, Oliveira R, et al. Antifungal activity of silver nanoparticles in combination with nystatin and chlorhexidine digluconate against Candida albicans and Candida glabrata biofilms. Mycoses. 2013; 56(6): 672-80.

4. Mijnendonckx K, Leys N, Mahillon J, Silver S, Van Houdt R. Antimicrobial silver: uses, toxicity and potential for resistance. Biometals. 2013; 26(4): 609-21.

5. Chen X, Schluesener HJ.Nanosilver: a nanoproduct in medical application. Toxicol Lett. 2008; 176(1): 1–12.

6. Wei L, Lu J, Xu H, Patel A, Chen ZS, Chen G. Silver nanoparticles: synthesis, properties, and therapeutic applications. Drug Discovery Today. 2015; 20(5): 595-601.

7. Benn T, Cavanagh B, Hristovski K, Posner JD, Westerhoff P. The release of nanosilver from consumer products used in the home. Journal of Environmental Quality. 2010; 39(6): 1875-82.

8. Massarsky A, Trudeau VL, Moon TW. Predicting the environmental impact of nanosilver. Environ Toxicol Pharmacol. 2014; 38(3): 861-73.

9. Ebabe Elle R, Gaillet S, Vidé J, Romain C, Lauret C, Rugani N, et al. Dietary exposure to silver nanoparticles in Sprague–Dawley rats: Effects on oxidative stress and inflammation. Food Chem Toxicol. 2013; 60: 297-301.

10. Schins RPF, Knaapen AM. Genotoxicity of poorly soluble particles. Inhalation Toxicology. 2007; 19(suppl 1): 189-98.

11. Hadrup N, Lam HR. Oral toxicity of silver ions, silver nanoparticles and colloidal silver- a review. Regul Toxicol Pharmacol. 2014; 68(1): 1-7.

12. McShan D, Ray PC, Yu H. Molecular toxicity mechanism of nanosilver. J Food Drug Anal. 2014; 22(1): 116–27.

13. Reidy B, Haase A, Luch A, Dawson KA, Lynch I. Mechanisms of silver nanoparticle release, transformation and toxicity: a critical review of current knowledge and recommendations for future studies and applications. Materials. 2013; 6(6): 2295-350.

14. Di Meo S, Reed TT, Venditti P, Victor MV. Harmful and Beneficial Role of ROS. Oxid Med Cell Longev. 2016; 2016.

15. Nićiforović N, Mihailović V, Mašković P, Solujić S, Stojković A, Muratspahić DP. Antioxidant activity of selected plant species; potential new sources of natural antioxidants. Food Chem Toxicol. 2010; 48(11): 3125-30.

16. Crozier A, Jaganath IB, Clifford MN. Dietary phenolics: Chemistry, bioavailability and effects on health. Nat Prod Rep. 2009; 26(8): 1001-43.

17. Wang YH, Wan ZL, Yang XQ, Wang JM, Guo J, Lin Y. Colloidal complexation of zein hydrolysate with tannic acid:

Constructing peptides-based nanoemulsions for alga oil delivery. Food Hydrocolloids. 2016; 54(part A): 40-8.

18. Sahiner N, Sagbas S, Aktas N, Silan C. Inherently antioxidant and antimicrobial tannic acid release from poly (tannic acid) nanoparticles with controllable degradability. Colloid Surf B: Biointerfaces. 2016; 142: 334-43.

19. Tikoo K, Sane MS, Gupta C. Tannic acid ameliorates doxorubicin-induced cardiotoxicity and potentiates its anti-cancer activity: potential role of tannins in cancer chemotherapy. Toxicol Appl Pharmacol. 2011; 251(3): 191-200.

20. Halkes CJM, Van Dijk H, De Jaegere PT, Plokker HWM, van Der Helm Y, Erkelens DW, et al. Postprandial increase of complement component 3 in normolipidemic patients with coronary artery disease: effects of expanded-dose simvastatin. Arterioscler Thromb Vasc Biol. 2001; 21(9), 1526-30.

21. Xiao H, Liu B, Mo H, Liang G. Comparative evaluation of tannic acid inhibiting α-glucosidase and trypsin. Food Res Int. 2015; 76(3): 605-10.

22. Fang N, Lee H, Sun C, Zhang X. Sub–diffraction-limited optical imaging with a silver superlens. Science. 2005; 308(5721): 534-7.

23. Sharma HS, Ali SF, Hussain SM, Schlager JJ, Sharma A. Influence of engineered nanoparticles from metals on the blood-brain barrier permeability, cerebral blood flow, brain edema and neurotoxicity. An experimental study in the rat and mice using biochemical and morphological approaches. J Nanosci Nanotechnol. 2009; 9(8): 5055-72.

24. Ahmad ST, Sultana S. Tannic acid mitigates cisplatin-induced nephrotoxicity in mice. Hum Exp Toxicol. 2012; 31(2): 145-56.

25. Tappel AL, Zalkin H. Inhibition of lipid peroxidation in mitochondria by vitamin E. Archives of Biochemistry and Biophysics. 1959; 80(2): 333-6.

26. Mishra HP, Fridovich I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. JBC. 1972; 247: 3170-5.

27. Chiu DTY, Stults FH, Tappel AL. Purification and properties of rat lung soluble glutathione peroxidase. Biochim Biophys Acta. 1976; 445(3): 558-66.

28. Habig WH, Pabst MJ, Jakoby WB. Glutathione S-transferases. The first enzymatic step in mercapturic acid formation. JBC. 1974; 249: 7130-9.

29. Luck H. Catalase. In: Bergmayer, M. V. (Ed.), Method of Enzymatic Analysis. Verlag Chemic. Academic Press, New. 1974; 885.

30. Jollow DJ, Michell JR, Zampaglionic N, Gillete JR. Bromoibenzene-induced Liver necrosis: Protective role of glutathione and evidence for 3,4-Bromobenzene oxide as hepatotoxic metabolite. Pharmacology. 1974; 11: 151-69.

31. Drury RA, Wallington EA, Carleton S. Histological Techniques, fifth ed., Oxford University Press, London, New York, Toronto. 1980; 241-2.

32. SAS, Statistical Analysis System. SAS Procedure Guide. Release 6.03 Edition. SAS Institute Inc., Cary, Nc, U.S.A. 1998.

33. Duncan DB. Multiple range and multiple F tests. Biometrics. 1955; 11(1): 1-42.

34. Garcia T, Lafuente D, Blanco J, Sanchez DJ, Sirvent JJ, Domingo JL et al. Oral subchronic exposure to silver nanoparticles in rats. Food Chem Toxicol. 2016; 92: 177-87.

35. Kovvuru P, Mancilla PE, Shirode AB, Murray TM, Begley TJ, Reliene R. Oral ingestion of silver nanoparticles induces genomic instability and DNA damage in multiple tissues. Nanotoxicology. 2015; 9(2): 162-71.

36. Sarhan OMM, Hussein RM. Effects of intraperitoneally injected silvernanoparticles on histological structures and blood parameters in the albino rat. Int J Nanomedicine. 2014; 9: 1505-17.

37. Burrell RE. A scientific perspective on the use of topical silver preparations. Ostomy Wound Manage. 2003; 49: 19-24.

38. Toh HS, Batchelor-Mcauley C, Tschulik K, Compton RG. Chemical interactions between silver nanoparticles and thiols: a comparison of mercaptohexanol against cysteine. Science China Chemistry. 2014; 57(9): 1199-210.

39. Nemenqani D, El-Gharib O, Ahmed AM, Baiuomy AR. The protective effects of antioxidant (vitamin C) against hepatic oxidative damage induced by zinc oxide nanoparticals. IRJABS. 2015; 9(4): 502-9.

40. Wang J, Asbach C, Fissan H, Hülser T, Kuhlbusch TA, Thompson D, et al. How can nanobiotechnology oversight advance science and industry: examples from environmental, health, and safety studies of nanoparticles (nano-EHS). J Nanopart Res. 2011; 13(4): 1373-87.

41. He W, Zhou YT, Wamer WG, Boudreau MD, Yin JJ. Mechanisms of the pH dependent generation of hydroxyl radicals and oxygen induced by Ag nanoparticles. Biomaterials. 2012; 33(30): 7547-55.

42. Yang EJ, Kim S, Kim JS, Choi IH. Inflammasome formation and IL-1â release by human blood monocytes in response to silver nanoparticles. Biomaterials. 2012; 33(28): 6858-67.

43. Rahman F, Chowdhury S, Rahman MM, Ahmed D, Hossain A. Antimicrobial resistance pattern of gram-negative bacteria causing urinary tract infection. Stamford journal of pharmaceutical sciences. 2009; 2(1): 44-50.

44. Loeschner K, Hadrup N, Qvortrup K, Larsen A, Gao X, Vogel U, et al. Distribution of silver in rats following 28 days of repeated oral exposure to silver nanoparticles or silver acetate. Particle Fibre Toxicology. 2011; 8(1): 18.

45. Casas-Grajales S, Muriel P. Antioxidants in liver health. World J Gastrointest Pharmacol Ther. 2015; 6(3): 59-72.

46. Skalska J, Dabrowska-Bouta B, Struzynska L. Oxidative stress in rat brain but not in liver following oral administration of a low dose of nanoparticulate silver. Food Chem Toxicol. 2016; 97: 307-15.

47. Yang ST, Wang X, Jia G, Gu Y, Wang T, Nie H, et al. Long-term accumulation and low toxicity of single-walled carbon nanotubes in intravenously exposed mice. Toxicol Lett. 2008; 181(3): 182-9.

48. Kim S, Choi JE, Choi J, Chung KH, Park K, Yi J, et al. Oxidative stress-dependent toxicity of silver nanoparticles in human hepatoma cells. Toxicology in vitro. 2009; 23(6): 1076-84.

49. Recknagel RO, Glende Jr EA, Dolak JA, Waller RL. Mechanisms of carbon tetrachloride toxicity. Pharmacol Ther. 1989; 43(1): 139-54.

50. Adeyemi OS, Whiteley CG. Interaction of nanoparticles with arginine kinase from Trypanosoma brucei: kinetic and mechanistic evaluation. International journal of biological macromolecules. 2013; 62: 450-6.

51. Guyton AC, Hall JE. Dominant role of the kidney in long-term regulation of arterial pressure and in hypertension: the integrated system for pressure control. Guyton & Hall: Textbook of Medical Physiology. 2000; 10: 195-209.

52. Venkatesan N, Punithavathi D, Arumugam V. Curcumin prevents adriamycin nephrotoxicity in rats. Br J Pharmacol. 2000; 129(2): 231–4.

53. Braydich-Stolle L, Hussain S, Schlager JJ, Hofmann MC. In vitro cytotoxicity of nanoparticles in mammalian germline stem cells. Toxicol Sci. 2005; 88(2): 412-9.

54. Albendea CD, Gómez-Trullén EM, Fuentes-Broto L, Miana-Mena FJ, Millán-Plano S, Reyes-Gonzales MC, et al. Melatonin reduces lipid and protein oxidative damage in synaptosomes due to aluminium. J Trace Elem Med Bio. 2007; 21(4): 261-8.

55. Ene-ojo AS, Chinedu EA, Yakasai FM. Toxic effects of sub-chronic administration of chloroform extract of Artemisia maciverae Linn on the kidney of Swiss albino rats. Int J Biochem Res Rev. 2013; 3(2): 119-28.

56. Sarkar D, Latif SA, Aich J, Uddin MM. Studies on serum Creatinine and Creatinine clearance in hypertensive patients. JBSP. 2006; 1: 19-26.

57. Adeyemi OS, Sulaiman FA. Biochemical and morphological changes in Trypanosoma brucei brucei-infected rats treated with homidium chloride and diminazene aceturate. Journal of basic and clinical physiology and pharmacology. 2012; 23(4): 179-83.

58. Adeyemi OS, Akanji MA. Psidium guajava leaf extract. Effects on rat serum homeostasis and tissue morphology. Comparative Clinical Pathology. 2010; 21(4): 401-7.

59. Naghsh N, Mashayekh AM, Khodadadi S. Effects of silver nanoparticle on lactate dehydrogenase activity and histological changes of heart tissue in male wistar rats. Journal of Fasa University of Medical Sciences. 2013; 2(4): 303-7.

60. Lovrić J, Bazzi HS, Cuie Y, Fortin GR, Winnik FM, Maysinger D. Differences in subcellular distribution and toxicity of green and red emitting CdTe quantum dots. J Mol Med. 2005; 83(5): 377-85.

61. Sharma V, Shukla RK, Saxena N, Parmar D, Das M, Dhawan A. DNA damaging potential of zinc oxide nanoparticles in human epidermal cells. Toxicol Lett. 2009; 185(3): 211-8.

62. Arora S, Jain J, Rajwade JM, Paknikar KM. Cellular responses induced by silver nanoparticles: in vitro studies. Toxicol Lett. 2008; 179(2): 93-100.

63. Tiwari R, Singh RD, Khan H, Gangopadhyay S, Mittal S, Singh V, et al. Oral subchronic exposure to silver nanoparticles causes renal damage through apoptotic impairment and necrotic cell death. Nanotoxicology. 2017; 11(5): 671-86.

64. Meng J, Ji Y, Liu J, Cheng X, Guo H, Zhang W, et al. Using gold nanorods core/silver shell nanostructures as model material to probe biodistribution and toxic effects of silver nanoparticles in mice. Nanotoxicology. 2014; 8(6): 686-96.

65. Guo H, Zhang J, Boudreau M, Meng J, Yin JJ, Liu J, et al. Intravenous administration of silver nanoparticles causes organ toxicity through intracellular ROS-related loss of interendothelial junction. Particle Fibre Toxicology. 2016; 13(1): 21.

66. Vivarelli M, Massella L, Ruggiero B, Emma F. Minimal Change Disease. Clin J Am Soc Nephrol. 2016; 27: 1811-22.

67. Kroemer G, El-Deiry WS, Golstein P, Peter ME, Vaux D, Vandenabeele P, et al. Classification of cell death: recommendations of the Nomenclature Committee on Cell Death. Cell Death Differ. 2005; 12(suppl 2): 1463-7.

68. Li L, Wu H, Peijnenburg WJ, Van Gestel CA. Both released silver ions and particulate Ag contribute to the toxicity of AgNPs to earthworm Eisenia fetida. Nanotoxicology. 2015; 9(6): 792-801.

69. Uchiumi F, Sato T, Tanuma SI. Identification and characterization of a tannic acid-responsive negative regulatory element in the mouse mammary tumor virus promoter. J Biol Chem. 1998; 273(20): 12499-508.

70. Andrade RG, Dalvi LT, Silva JMC, Lopes GK, Alonso A, Hermes-Lima M. The antioxidant effect of tannic acid on the in vitro copper-mediated formation of free radicals. Arch Biochem Biophys. 2005; 437(1): 1-9.

Correspondence to/Autor za korespondenciju
Dr. Israa F. Mosa
Ph. D. in Biological Sciences, Department of Environmental Studies,
Institute of Graduate Studies and Research, Alexandria University, Alexandria, Egypt
Teachingstaff at the Faculty of Education, Department of Natural Science,
Alexandria University, Egypt
Mobile: +20 – 01024680746
E-mail address: Israa_fat7y@yahoo.com

SANAMED
2019; 14(2): 147–152
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i2.310
UDK: 616.718.5-001.5-089
ID: 278328588
Original article

COMPARISON OF SURGICAL TREATMENT RESULTS AND CLINICAL AND RADIOLOGICAL FINDINGS OF TIBIAL PLATEAU FRACTURES

Kehribar Lokman,[1] Karapinar Levent[2]

[1] Department of Orthopedics and Traumatology, Gazi State Hospital, Samsun, Turkey
[2] Tepecik Training and Research Hospital Izmir, Turkey

Primljen/Received 23. 01. 2019. god.

Prihvaćen/Accepted 16. 04. 2019. god.

Abstract: **Introduction:** In this retrospective study, it was aimed to evaluate the correlation between operative treatment results and clinical and radiological findings of tibial plateau fractures.

Patients and Methods: Between 1996 and 2006, 33 knees were operated for tibia plateau fracture of 32 patients. 29 patients were male and 3 were female. Only 3 cases (9.99%) were open tibial plateau fractures. The mean age was 45 years. Fractures classified using the Schatzker classification were: 17 (52%) type 1, 12 (12%) type 2, 9 (27%) type 5 and 6 (9%) type 6. Patients following the period were at least 44 weeks and maximum 480 weeks (mean 60 weeks).

Results: The results of 33 patients were determined by the clinical and radiological system of Rasmussen. According to clinical findings, 17 cases were excellent, 9 were good, 6 were medium and 1 was poor. According to the radiological findings, 9 cases were excellent, 16 were good, 6 were medium and 2 were bad. The difference between clinical and radiological findings was analyzed with Pearson core analysis and statistically significant ($p < 0.005$). Comparison was made according to the time between injury and operation and no statistically significant difference was found ($p > 0.005$). The analyzes of the grade of fracture and the degree of fracture were statistically significant ($p < 0.005$). 42.4% of all patients had meniscus injury. Therefore, arthroscopy should be used with surgery.

Conclusion: Anatomic reduction, rigid fixation of the joint and early mobilization can reduce complications and improve the function of the knee joint in tibial plateau fractures.

Key Words: Anatomic reduction, tibial plateau fracture, surgery.

INTRODUCTION

The knee joint is one of the strongest and important joints of the body and is directly affected by plateau fractures. As these fractures are intra-articular in nature, they affect the alignment, stability, and movement of the joint. In addition, as the knee is a complex joint with dense soft tissues,its related injuries are classified as complex injuries. The mechanism of fracture is mainly due to axial compressive forces with varus or valgus stress and these fractures are produced by high-energy traumas (1). The Schatzker classification, which was developed in 1979 based on the anteroposterior (AP) radiographs of a series of 94 patients, has been still widely used by orthopedic surgeons. This system classify tibial plateau fractures into six types and lateral plateau fractures typically present with depression, while medial plateau fractures typically present with split (2). In addition, these fractures usually lead to arthrosis of the knee joint and total knee arthroplasty is a usually performed procedure following the arthrosis after tibial plateau fractures (3, 4).

The main goal of treatment of plateau fractures is to recover the integrity of the articular surface and to improve the function of the articular activity with minimal injury. In 1825, Sir Astley Cooper first published experiences with a series of knee dislocations and treated tibial fractures with compressive bandage and early passive mobilization, irrespective of the fracture pattern (5). Later in the history, open reduction and plate-screw fixation and osteosynthesis gain popularity which is still the first-line treatment in tibial plateau fracture practice (6, 7).

In the present study, we present our experience with tibial plateau fractures and discuss the treatment approaches in the light of the literature data.

PATIENTS AND METHODS

This retrospective study included a total of 33 knees of 32 patients who were operated due to tibial plateau fractures at No. 1 Orthopedics and Traumatology inpatient clinic of Izmir Tepecik Training and Research Hospital, Izmir, Turkey between 1996 and 2006. A written informed consent was obtained from each patient. The study protocol was approved by the Local Ethical Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

According to the Schatzker classification, 17 cases were type I, four cases were type II, nine cases were type V, and three cases were type VI. Among all fractures, there were three open fractures. The most common cause was pedestrian accidents.

Seventeen knees were surgically treated with a percutaneous technique. A lateral and anterolateral incision was made in 13 patients, while an anteromedial incision was made in one patient. Extensile surgery was performed in one patient. No parapatellar incision was used in any of the patients. Grafting was applied in 12 patients. All grafts were spongious and harvested from the same side of the iliac crest. Postoperatively, partial weight bearing was allowed at 13 weeks, while full weight bearing was allowed at 18 weeks.

The modified Rasmussen's clinical and radiological criteria were used to evaluate the tibial plateau fractures. It consists of five categories including pain, walking capacity, extension, total range of motion, and stability. The total score is the sum of these five items, and the higher scores indicate the greater function. A score of 0-9 is defined as poor, 10-19 as fair, 20-26 as good, and 27-30 as excellent. In addition, the anatomical score consists of three categories including depression, condylar widening, and angulation. A score of 0-5 is defined as poor, 6-11 as fair, 12-17 as good, and 18 as excellent.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 10.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation (SD), number and frequency. The Pearson's correlation analysis was used for radiological and clinical comparisons. The Kruskal-Wallis test was carried out to compare radiological and clinical scores according to the Schatzker classification. The Mann-Whitney U test was used for binary comparisons. A p value of < 0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Of the patients, 29 (87.9%) were males and three (12.1%) were females. The mean age was 45 (range, 18 to 63) years. The mean follow-up was 65 (range, 11 to 120) months.

According to the Rasmussen's radiological criteria, the mean score was 13.6 (range, 4 to 18) in all 33 knees. The result was excellent in nine (27.3%), good in 16 (48.5%), and poor in six (6.0%) cases (Figure 1). According to the Rasmussen's clinical criteria, the mean score was 23.3 (range, 8 to 29). The result was excellent in 17 (51.5%), good in nine (27.3%), fair in six (18.2%), and poor in one (3%) cases (Figure 2).

In the radiological evaluation of the final AP and lateral graphies, the degree of depression, condylar widening, and angulation were calculated. The mean degree of depression was 3.87 mm, the mean condylar widening was 4.1 mm, and the mean angulation was

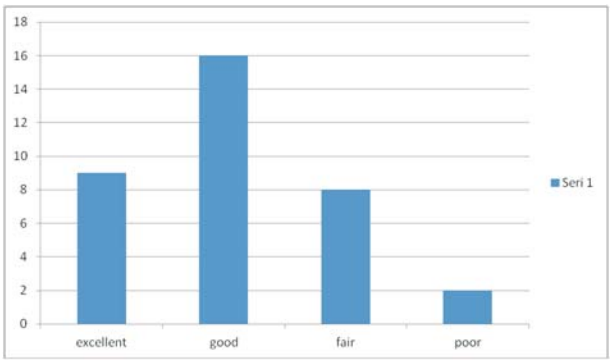


Figure 1. Rasmussen's radiological scores

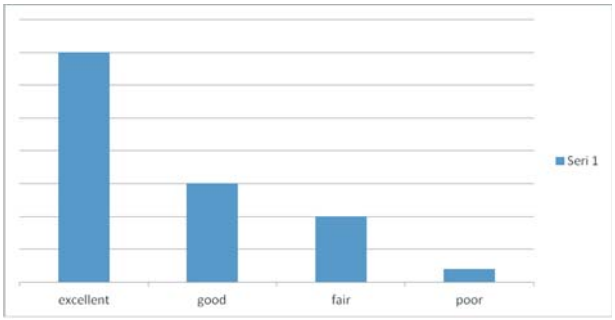


Figure 2. *Rasmussen's clinical scores*

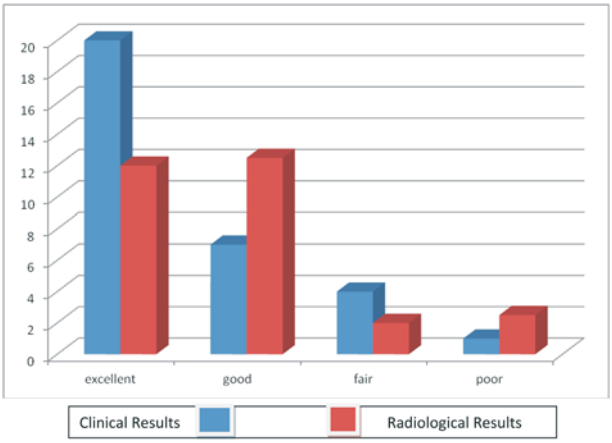


Figure 3. *Comparison of the Rasmussen's clinical and radiological results*

3.7 in favor of valgus. In the final clinical evaluation, the mean extension loss was 7.3° and the mean range of motion was 128°. In all patients, the knee was stable at 20° flexion and full extension.

Based on the comparison of the clinical and radiological results, the clinical status of the patients was found to be correlated with the radiological status. In 12 patients (36.4%), the clinical status was better than the radiological status, while the clinical and radiological statuses were equivalent in the remaining 19 patients (57.6%) (Figure 3).

The Pearson's correlation analysis showed a positive correlation between the clinical scores and radiological scores ($r = 0.754$, $p < 0.001$). In addition, according to the degree of depression (0-5 mm, 6-9 mm, or ≥ 10 mm), the mean clinical score was 25.947 and the mean radiological score was 5.789 in the 0-5 mm group (n = 19). In the 6-9 mm group (n = 10), the mean clinical score was 0.500 and the mean radiological score was 12.4. Finally, the mean clinical score was 12.500 and the mean radiological score was 8.250 in the ≥ 10 mm group (n = 4). According to the Kruskal-Wallis test, there was a significant difference in the clinical and radiological scores among the depression groups, indicating that the clinical and radiological scores decreased, as the degree of depression increased ($p < 0.001$ for both) (Figure 4).

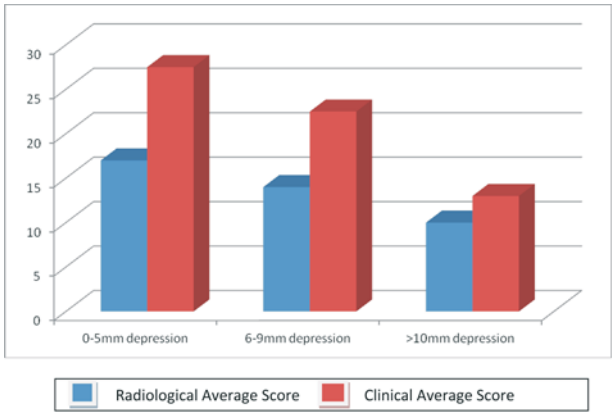


Figure 4. *Clinical and radiological results according to depression degree*

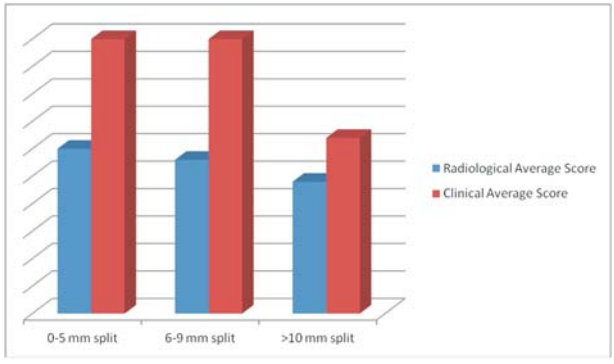


Figure 5. *Clinical and radiological results according to split*

According to the degree of cleavage (0-5 mm, 6-9 mm, or ≥ 10), the mean clinical score was 24.250 and the mean radiological score was 15.375 in the 0-5 mm group (n = 16). In the 6-9 mm group, the mean clinical score was 24.091 and the mean radiological score was 13.818 (n = 11). Finally, the mean clinical score was 15.833 and the mean radiological score was 9.167 in the ≥ 10 mm group (n = 6). According to the Kruskal-Wallis test, there was a significant difference in the clinical ($p = 0.022$) and radiological scores ($p = 0.019$) among the cleavage groups, indicating that the clinical and radiological scores decreased, as the degree of cleavage increased (Figure 5).

DISCUSSION

Tibial plateau fractures are complex injuries involving not only the bone structure, but also the other connective tissue components such as the joint cartilage and meniscus, as they are intra-articular in nature.Considering the risk of osteoarthritis and degeneration, treatment of these fractures is of utmost importance.

Osteoporosis is a risk factor in tibial plateaufractures. In a case series, Su et al. reported osteoporosis were seen adult women aged ≥ 50 years following the tibial plateaufractures (8). In our series, however, the number of female patients is not consistent with the literature with a male ratio of 87.9% and female ratio of 12.1%. This discrepancy can be explained by the fact that our facility is a complex trauma center.

In the literature, there is no consensus on the surgical treatment of these fractures. Some authors have recommended conservative treatment, irrespective of the type of the fracture and advocated that reduction with conservative treatment yields satisfactory functional outcomes, but not anatomical outcomes (9, 10). On the other hand, some others have recommended surgical treatment, except for stable, non-displaced fractures. Surgery has several advantages including a smooth reduction of the joint surface, anatomical restoration of the limb axis, and stabile fixation with early mobilization. It is also indicated in the treatment of connective tissue and meniscus injuries which majorly affect the functional and anatomical outcomes (11, 12).

There are studies in the literature that they found no significant relationship between the depression and functional outcomes in the majority of cases with ≥ 10 mm depression at the final visit (13, 14). However, Singleton et al. found a significant relationship between the degree of depression and uncorrectable valgus deformity and secondary osteoarthritis (4). In a case series including 60 patients, Blokker et al.achieved satisfactory results in 85% of cases undergoing anatomic reduction and in 75% of cases in a step of less than 5 mm, although a step of greater than 5 mm was associa-

ted with unsatisfactory results (15). In our study, we classified the degree of depression as 0-5 mm, 6-9 mm, and ≥ 10 mm and found poor clinical and radiological results with increased depression.

Rasmussen found a close relationship between varus angulation and osteoarthritis and suggested that alignment of the medial condyle, particularly,should be proper in double condylar fractures. In addition, the author reported that an evident malalignment of the tibial plateau surface and femoral condyle with uncorrectable tibial condylar widening was significantly associated with secondary osteoarthritis (16). In our study, good and excellent clinical and radiological outcomes were achieved in 72.7% of the patients. However, poor clinical and radiological results were obtained in one patient and two patients, respectively. In their study, Schatzker et al. also achieved acceptable outcomes in 32 of 94 (78%) surgically treated patients and suggested that osteoporosis was a major factor affecting the outcome (2). In another case series involving 95 patients, Waddel et al. applied surgical treatment to 69 patients and achieved satisfactory results in 65% of these patients (17). Also, the authors further claimed that improved results could be obtained with grafting combined with internal fixation.

In the present study, postoperative complications were seen in three patients (9.09%) including deep vein thrombosis in one patient and superficial infection in two patients. None of the patients experienced compartment syndrome, heterotopic ossification, or vessel injury. In a study, Kayiran et al. reported that the most common postoperative complication was heterotopic ossification (18). In another study, Rockwood found infection to be the major complication following surgery. To prevent infections, duration of surgery should be diminished, extraperiosteal dissection should be avoided, and prophylactic antibiotic therapy should be given (19). In our study population, one patient had a peroneal lesion preoperatively. Although the lesion was intraoperatively explored and released, the nerve function remained impaired. Of note, the lack of deep vein thrombosis or pulmonary embolism in any of the patients in our study, which are commonly reported in the literature, can be explained by individual genetic factors and the use of low-molecular-weight heparin prophylaxis in all patients.

Nonetheless, there are some limitations to this study. First, the results cannot be generalized to the overall population due to the small sample size and retrospective nature of the study. Second, there are many factors influencing the results of tibial plateau fractures.

In conclusion, clinicians should keep in mind that good clinical results can be achieved with surgery in tibial plateau fractures, even if radiological results are poor and, therefore, evaluation should not be based on radiological criteria alone. Based on our experience, we suggest anatomical and rigid fixation in the treatment of these fractures to provide early mobilization and to minimize dysfunction. However, further large-scale, long-term studies are needed to establish a conclusion.

Acknowledgment: None

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Licensing

Case Sample

46 years old male, Car accident, Schatzker Type 6 fracture

Preoperative, early postoperative and 1 year follow up X-rays are shown below

Sažetak

UPOREĐIVANJE REZULTATA HIRURŠKOG TRETMANA I KLINIČKIH I RADIOLOŠKIH NALAZA KOD PRELOMA TIBIJALNOG PLATOA

Kehribar Lokman,[1] Karapinar Levent[2]

[1] Department of Orthopedics and Traumatology, Gazi State Hospital, Samsun, Turkey
[2] Tepecik Training and Research Hospital Izmir, Turkey

Uvod: U ovoj retrospektivnoj studi, cilj je bio da se ispita korelacija između rezultata operativnog tretmana i kliničkih i radioloških nalaza kod preloma platoa tibije.

Pacijenti i metode: U periodu od 1996. do 2006. godine, 33 kolena su operisana zbog preloma platoa tibije kod 32 pacijenta. 29 pacijenata su bili muškog pola, a troje je bilo ženskog. Samo 3 slučaja (9.99%) je imalo otvoreni prelom platoa tibije. Prosečna starost iznosila pacijenata je bila 45 godina. Prelomi su klasifikovani koristeći Schatzker klasifikaciju i pokazali su sledeće rezultate: 17 (52%) imalo je tip 1, 12 (12%) je imalo tip 2, 9 (27%) tip 5 i 6 (9%) imalo je tip 6. Pacijenti su praćeni u periodu od minimum 44 nedelje, maksimalno 480 nedelja (srednja vrednost je 60 nedelja).

Rezultati: Rezultati 33 operisana kolena su utvrđeni na osnovu kliničkog i radiološkog sistema Rasmussen. Prateći kliničke nalaze, 17 slučajeva se odlično oporavilo, 9 je bilo dobro, 6 je bilo osrednjje i 1 je bio loš. Prema radiološkim nalazima, 9 slučajeva je bilo u odličnom stanju, 16 je bilo dobro, 6 je bilo osrednje i 2 su bila lošeg stanja. Razlika između kliničkih i radioloških nalaza je analizirana Pirsonovom core analizom i određivana je statistička značajnost ($p < 0,005$). Razlika je određivana prema vremenu između povrede i operacije i nije nađena nikakva statistička značajnost ($p > 0,005$). Analize stadijuma i stepena preloma su pokazale statističku značajnost među grupama ($p > 0,005$). 42,4% svih pacijenata je imalo povredu meniskusa. S toga, artroskopija bi trebalo da se koristi u operativnom lečenju ovog oboljenja.

Zaključak: Anatomska redukcija, rigidno fiksiranje zgloba i rana mobilizacija mogu da smanje nivo komplikacija i da poboljšaju funkciju zgloba kolena kod preloma platoa imatibije.

Ključne reči: anatomska redukcija, prelom platoa tibije, hirurgija.

REFERENCES

1. Pean CA, Driesman A, Christiano A, Konda SR, Davidovitch R, Egol KA. Functional and clinical outcomes of nonsurgically managed tibial plateau fractures. J Am Acad Orthop Surg. 2017; 25(5): 375-80.

2. Schatzker J, McBroom R, Bruce D. The tibial plateau fracture. The Toronto experience 1968-1975. Clin Orthop Relat Res. 1979 (138): 94-104.

3. Abdel MP, von Roth P, Cross WW, Berry DJ, Trousdale RT, Lewallen DG. Total knee arthroplasty in patients with a prior tibial plateau fracture: a long-term report at 15 years. J Arthroplasty. 2015; 30(12): 2170-2.

4. Singleton N, Sahakian V, Muir D. Outcome after tibial plateau fracture: how important is restoration of articular congruity? J Orthop Trauma. 2017; 31(3): 158-63.

5. Cooper A, Tyrrell F. The lectures of Sir Astley Cooper on the principles and practice of surgery: Sherman; 1826.

6. Van Dreumel R, Van Wunnik B, Janssen L, Simons P, Janzing H. Mid-to long-term functional outcome after open reduction and internal fixation of tibial plateau fractures. Injury. 2015; 46(8): 1608-12.

7. Musahl V, Tarkin I, Kobbe P, Tzioupis C, Siska P, Pape H-C. New trends and techniques in open reduction and internal fixation of fractures of the tibial plateau. J Bone Joint Surg Br. 2009; 91(4): 426-33.

8. Su EP, Westrich GH, Rana AJ, Kapoor K, Helfet DL. Operative treatment of tibial plateau fractures in patients older than 55 years. Clin Orthop Relat Res. 2004; 421: 240-8.

9. Chauhan A, Slipak A, Miller MC, Altman DT, Altman GT. No Difference Between Bracing and No Bracing After Open Reduction and Internal Fixation of Tibial Plateau Fractures. JAAOS-Journal of the American Academy of Orthopaedic Surgeons. 2018; 26(6): e134-41.

10. Shrestha R, Kandel M, Gupta HK, Shrestha SK, Dongol S, Hamal RR. A study of conservative management of tibial plateau fractures. Journal of College of Medical Sciences-Nepal. 2016; 12(1): 5-9.

11. Chen XZ, Liu CG, Chen Y, Wang LQ, Zhu QZ, Lin P. Arthroscopy-assisted surgery for tibial plateau fractures. Arthroscopy. 2015; 31(1): 143-53.

12. Warner SJ, Garner MR, Schottel PC, Fabricant PD, Thacher RR, Loftus ML, et al. The effect of soft tissue injuries on clinical outcomes after tibial plateau fracture fixation. J Orthop Trauma. 2018; 32(3): 141-7.

13. Li D, Fang Y, Liang Y, Ma K, Zou C. Postoperative computed tomography evaluation of posterior tibial plateau fractures: mean 7-Year clinical follow-up. J Knee Surg. 2018; 31(7): 670-6.

14. Patel P, Trivedi K, Kumar P, Mehrotra R, Chaudhary D, Chaudhary P, et al. Assessment of Functional and Radiological Outcome of Proximal Lateral Condyle Fracture of Tibia (Schatzker Type 1, 2 and 3) Fixed with Locking Compression

Plate and Screw. Indian Journal of Public Health Research & Development. 2018; 9(5): 279-83.

15. Blokker CP, Rorabeck CH, Bourne RB. Tibial plateau fractures. An analysis of the results of treatment in 60 patients. Clin Orthop Relat Res. 1984; 182: 193-9.

16. Rasmussen PS. Tibial condylar fractures: impairment of knee joint stability as an indication for surgical treatment. J Bone Joint Surg Am. 1973; 55(7): 1331-50.

17. Stevens DG, Beharry R, McKee MD, Waddell JP, Schemitsch EH. The long-term functional outcome of operatively treated tibial plateau fractures. J Orthop Trauma. 2001; 15(5): 312-20.

18. Kayıran E, Orhan Z, Parmaksızoğlu A, Erdemir A. Yazıcı N. Tibia plato kırıklarının cerrahi tedavisinde sonuçları etkileyen faktörler. Acta Orthop Traumatol Turc. 2000; 34: 34-9.

19. Papagelopoulos PJ, Partsinevelos AA, Themistocleous GS, Mavrogenis AF, Korres DS, Soucacos PN. Complications after tibia plateau fracture surgery. Injury. 2006; 37(6): 475-84.

Correspondence to/Autor za korespondenciju
Lokman Kehribar
Gazi State Hospital, Department of Orthopedics and Traumatology
Samsun, Turkey
e-mail: lokmankehribar@gmail.com
GSM: +90 553 590 37 29

SANAMED
2019; 14(2): 153–161
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i2.316
UDK: 618.1:[616.988:578.827; 615.371
ID: 278327564
Original article

PREDICTORS AND ACCEPTABILITY OF HUMAN PAPILLOMA VIRUS VACCINE UPTAKE AMONG SENIOR SECONDARY SCHOOL STUDENTS IN ILE-IFE

Fehintola O Funmito,[1] Fehintola O Akintunde,[2] Ogundele A Olorunfemi,[3] Adegbenro A Caleb,[1] Olowookere A Samuel,[1] Afolabi T Olusegun[1]

[1] Department of Community Health Obafemi Awolowo University, Ile-Ife, Nigeria
[2] Department of Obstretrics and Gyneacology Department Obafemi Awolowo University, Ile-Ife, Nigeria
[3] Department of Community Health and Primary Care, State Specialist Hospital, Ondo City, Nigeria

Primljen/Received 31. 01. 2019. god. Prihvaćen/Accepted 26. 05. 2019. god.

Abstract: **Introduction:** Cervical cancer is the second most common cancer in women worldwide and in Nigeria. Human papilloma virus (HPV), has been implicated as the causative agent of cervical cancer. The fact that HPV vaccination can prevent the occurrence of this deadly cancer is well established. Though the vaccine has been licensed in Nigeria since 2009 with widespread availability, it is yet to be included in National immunization program in Nigeria. This study aimed to assess the predictors and acceptability of the HPV vaccine among senior secondary girls in Ile-Ife.

Methods: This descriptive cross-sectional study recruited 400 students randomly selected from various secondary schools in Ife central-local government. The data was collected with the use of a pre-tested interviewer-administered questionnaire on knowledge, attitude, and acceptability of cervical cancer, HPV and HPV vaccine. Data were analyzed using descriptive and inferential statistics.

Results: Most respondents (93.2%) had poor knowledge of cervical cancer, HPV and HPV vaccine. Attitude towards cervical cancer and HPV vaccine was good and the majority (74.5%) had high acceptability for the HPV vaccine. Only 2.8% of the respondents have been vaccinated. Predictors of acceptability of HPV vaccine were younger age group ((AOR) 4.05, CI = 2.30-5.45), good knowledge ((AOR = 2.50, CI = 2.31-6.83), mother' higher level of education (AOR = 1.55, CI = 2.62- 4.58), perceived fatality of cervical cancer (AOR = 4.13, CI = 1.49 – 4.19) and perceived efficacy of the HPV vaccine (AOR = 1.57, CI = 0.49 – 3.18).

Conclusions: The knowledge of secondary school girls in the study area on cervical cancer, HPV and HPV vaccine is poor though the HPV vaccine acceptability is high. The high acceptability of the vaccine in this study is a reflection of the willingness of this vulnerable group to learn more about the subject matter. There is the need to create school health programs that will focus on health educating the students on this preventable cancer and the available vaccine. Including HPV vaccine into National immunization program in Nigeria may also improve awareness of cervical cancer and the vaccine uptake.

Key words: Knowledge, acceptability, HPV vaccine, senior secondary school.

INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide and in Nigeria. Most cervical cancer is caused by the human papilloma virus (HPV), a sexually transmitted infection, for which a vaccine is now available. About 47.72 million Nigerian women are at risk of cervical cancer and the crude incidence per 100,000 population is 17.1 while the age-standardized incidence per 100,000 population is 29.0 (1). Nigeria has a cervical cancer mortality rate of 22.9 deaths per 100,000 (1). About 50–80% of sexually active women are exposed to at least one HPV type during their lifetime (2, 3). Women are usually infected with HPV in their teens the to early 30s and cervical cancer is a rare complication of the STI which is common (3). The peak incidence of HPV infection occurs in most populations within 5–10 years of the first sexual experience and the highest prevalence rates are seen in women aged 20–24 years (4, 5). The key to reducing cervical

cancer morbidity and mortality is early detection and treatment of cervical precancerous lesions. Screening for cervical cancer is very important in order to detect a pre-clinical phase or early stages of a disease for the purpose of identifying those likely or unlikely to have a disease. It also improves the prognosis for treated cases, reduces morbidity after treatment of screen detected cases, reassured those with negative tests and also is cost-effective in terms of use of health care resources. Health promoting measures against cancer have led to the development of a vaccine against HPV, which is currently available and has been demonstrated to be safe and clinically effective (6, 7). Two HPV vaccine types are available for the prevention of HPV-related diseases: Gardasil and Cervarix. The quadrivalent vaccine (Gardasil) targets HPV types 6, 11, 16 and 18, and is 98% effective while the bivalent vaccine (Cervarix) targets HPV types 16 and 18 and is 92% effective (8, 9). The vaccines have also been shown to prevent precursors to some other cancers associated with HPV. They are targeted at females aged 9-26 years as the vaccines only work if given before infection occurs at all, therefore girls are targeted before their sexual debut (10, 11). The vaccines have been proven to be effective for at least 4-6years. The HPV vaccine was licensed in Nigeria in 2009 (12). HPV vaccination is targeted mainly at adolescents and the spread of information to this age-group has been cited as a major challenge for health professionals (13).

Several studies have been done among university undergraduates and mothers of under five on knowledge, attitude, and acceptability of HPV vaccine (14, 15 16). These studies revealed that knowledge was poor especially in developing countries but variable levels of acceptability of the vaccine (14, 15, 16). Few studies done among secondary school students on knowledge of cervical cancer and acceptability of human papilloma virus vaccine revealed that knowledge of HPV, cervical cancer and HPV vaccine was poor but willing to be vaccinated high these studies were done outside Nigeria (17, 18). Miri, Sarawak in Malaysia revealed that 61.8 % of respondents had poor knowledge level of cervical cancer and its prevention. The studies on undergraduates targeted older, mature population who have had a sexual debut. This limited those researches as the HPV vaccine is ideal for females (between the ages 9-26 years) who have not had sexual exposure. Many women who have lost their lives to cervical cancer could have been saved through vaccination before infection, screening, and treatment of precancerous lesions. Hence, the need for this study which is focusing on females in senior secondary school to assess their knowledge acceptability and predictors of the HPV vaccine. This study will also serve as a baseline for educating Nigeria adolescents on complications of the disease and the benefits of vaccination.

METHODS

Study location

This cross-sectional study was conducted among female students in selected public and private schools in Ife- Central Local Government Area (LGA) of Osun State, southwest Nigeria. Ile-Ife lays between latitude 7°28' N and longitude 4°33' E and had an area of 111km (3 square meters) with a population of 167,254 people according to 2006 census. It is regarded as the source of Yoruba ethnicity and the dominant language was Yoruba. It also serves as a commercial center with several commercial and cooperative banks, state and federal hospitals, private and federal schools and universities. Ife central-local government have 4 public and 23 private secondary schools. Each Secondary school is divided into Junior Secondary School (JSS) and Senior Secondary Schools (SSS). The sample size was determined using Fisher's formula (19). A total of 400 respondents from SSS were selected for the study using a multi-stage sampling method. Students whose assent and parental consent were obtained were recruited into the study.Permission was also obtained from the school authority. Students with a significant physical or mental handicap, which could affect their ability to respond validly to the study instrument, were excluded from the study.

The multi-stage sampling method was used to select eligible respondents over a period of one month. In the first stage, 2 public secondary schools were selected by balloting from the list of four public secondary schools and four private schools from the list of 23 private schools within Ife-central LGA. The number of respondents per school was proportionate to their population sizes. In the selected schools the list of all girls in all the arms in Senior Secondary Schools (SSS) were collected from the class teachers. The girls were recruited from SSS class 1 to 3 into the study using a systematic sampling technique until the desired sample size from each school was reached. Sampling interval was calculated by dividing the total number of students to be recruited from the school by the total number allotted to a class. The first participant was selected using simple random method (by balloting).

Data collection method and instrument

Data were collected using facilitated self-administered questionnaire with several questions adapted from previous studies (17, 20). The questionnaire was translated from English to Yoruba through a two-way process for students who may find the instrument easi-

er to complete in the local language. Questions were asked about respondents' socio-demographic characteristics as well as their, knowledge, attitude on cervical cancer, human papilloma virus vaccine and acceptance of HPV vaccine. All the information was collected in class under the supervision of trained research assistants in the absence of the teachers. Students' knowledge score was calculated out of the 14 knowledge specific questions. Each correct response earned one point, whereas any wrong response attracted no mark. Good knowledge on cervical cancer, human papilloma virus, and human papilloma virus vaccine was given to those respondents who scored greater than or equal to the mean, and poor knowledge on cervical cancer, human papilloma virus, and human papilloma virus vaccine was given to those respondents who scored below the mean score. Students' acceptability of human papilloma virus vaccine score was calculated out of the acceptability specific questions. Each correct response earned one point, whereas any wrong response attracted no mark. High acceptability of human papilloma virus vaccine was given to those respondents who scored above mean score and low acceptability score was given to those respondents who scored below mean score. The instrument was pretested among 20 students in Ife north local government. This was to assess the clarity of the questions and identify ambiguous questions. Permission was obtained from the local inspectorate officers head office in Osogbo and the school authorities of the respective schools used for the study. Informed consents (written) was obtained from the parents and assents from the participants. Participation was entirely voluntary and confidentiality was ensured; codes rather than participants' names were used for individual identification and were stored in a computer that was only accessible to the principal investigator.

Statistical analysis

After data collection, each questionnaire was given a unique code and entered into Statistical Package for Social Sciences (SPSS) version 20. Frequencies of variables were used to check for missed values and outliers. Any error identified at this time was corrected after revision of the original data using the code numbers. Descriptive analysis was used for the socio-demographic characterization of the respondents and other relevant variables (age, sex, education, marital status etc). Chi-square test was used to identify factors associated with students' knowledge of cervical cancer and human papilloma virus vaccine and factors influencing the acceptability of the human papilloma virus vaccine. Logistic regression was used to identify factors predicting the acceptability of HPV vaccine. For all statistical analysis, a P value less than 0.05 was considered significant.

RESULTS

Sociodemographic characteristics of respondents

Majority of the respondents (68.8%) are within the age range 13-15 years. The mean age of respondents was 15 ± 1.2 years. Majority of the respondents (51.2%) are in SS1. Eighty-six percent of the respondents were Yorubas and majority of the respondent parents had a tertiary level of education (70% of respondent fathers and 66% of respondent mothers) (Table 1).

Table 1. *Sociodemographic characteristics of respondents*

Variables	Frequency (%)
Age (years)	**Mean age = 15 ± 1.2 years**
10-12	16 (4)
13-15	275 (68.8)
16-18	107 (26.8)
19-21	2 (0.5)
Total	400 (100)
Class	
SSS1	205 (51.2)
SSS2	195 (48.8)
Total	400 (100)
Religion	
Christianity	291 (72.8)
Islam	109 (27.2)
Total	400 (100)
Ethnicity	
Yoruba	344 (86.0)
Igbo	42 (10.4)
Hausa	14 (3.6)
Total	400 (100)
Fathers educational status	
None	5 (1.2)
Primary	17 (4.4)
Secondary	98 (24.4)
Tertiary	280 (70)
Total	400 (100)
Mothers educational status	
None	11 (2.8)
Primary	18 (4.4)
Secondary	107 (26.8)
Tertiary	264 (66)
Total	400 (100)

Knowledge of HPV, Cervical Cancer & HPV vaccine among respondents

Few of the respondents (13.6%) had ever heard of human papilloma virus. About 30% of respondents have heard about cervical cancer and 41.4% said HPV vaccine is for sexually active people. Majority of the respondents (48.6%) said HPV vaccine should be given at age > 26 years. The overall majority of the respondents 93.2% have poor knowledge of HPV, cervical cancer and the HPV vaccine (Table 2).

Table 2. *Awareness, Knowledge of HPV, Cervical Cancer &HPV vaccine among Respondents*

Variables	Frequency (%)
Do you know about HPV? (n = 400)	
Yes	54 (13.6)
No	346 (86.4)
If yes how is it transmitted	
Shaking of hands with infected persons	15 (27.8)
Sexual intercourse	30 (55.6)
Sharing of sharp objects	9 (16.6)
Do you know about cervical cancer?	
Yes	122 (30.4)
No	278 (69.6)
HPV vaccine is only for people who are sexually active (n = 29)	
Yes	12 (41.4)
No	17 (58.6)
Risk Factors for Cervical Cancer*	
Family history	75 (18.8)
Early sexual exposure (before age sixteen)	91 (22.8)
Multiple sexual partners	84 (21.2)
Smoking	54 (13.6)
Prolong use of oral contraceptive pills	64 (16.0)
Old age	41.6 (10.4)
Infection with HPV	85 (21.2)
At what age should human papilloma virus vaccine be given? (n = 74)	
8-26 years	13 (17.6)
> 26 years	36 (48.6)
Don't know	22 (29.7)
Knowledge Score	
Good knowledge	27 (6.8)
Poor knowledge	373 (93.2)

Sources of information on cervical cancer and Human Papilloma Virus Vaccine

From Figure 1, the most common source of information on cervical cancer and HPV vaccines was the internet (38.5% and 31.0% respectively). Other common sources of information were through Mass Media (24.6% cervical cancer and 27.6% for the vaccine), schools (15.6% and 13.8% respectively), and their family members.

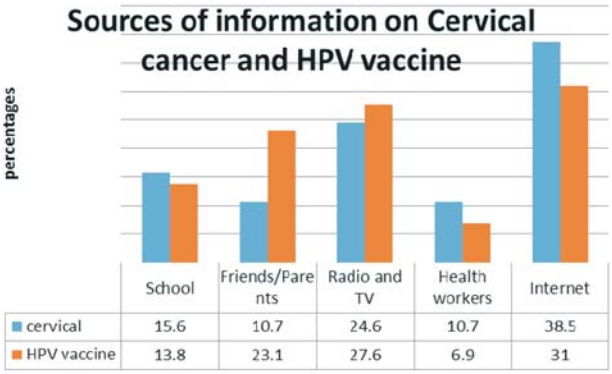


Figure 1. *Sources of information on Cervical cancer and HPV vaccine*

The attitude of respondents to cervical cancer, HPV and HPV vaccine

More than three-quarters of the respondents said education on HPV vaccine should be implemented in schools. One-third of the respondents agreed that cervical cancer is a big problem for women and that it causes death. Half of the respondents said it is preferable to vaccinate men and women with the HPV vaccine. About 43.5% and 42.5% of the respondents said HPV vaccine is safe and highly effective. Majority of the respondents (80.8% and 74.8%) agreed they don't have sufficient information on HPV and that HPV vaccination cannot lead to increase risky sexual behavior. The overall majority of the respondents have a good attitude towards HPV vaccine and cervical cancer (Table 3).

Table 3. *Attitude of respondents to cervical cancer, HPV and HPV vaccine*

Perception/Attitude To Cervical Cancer & Hpv Vaccine	Frequency (%)
Education on HPV should be implemented at school	
Yes	312 (78.0)
No	88 (22.0)
Cervical cancer is a big problem for women	
Yes	261 (65.2)
No	139 (34.8)
Cervical cancer can cause death for women	
Yes	240 (60)
No	160 (40)
It is preferable to vaccinate both men and women	
Yes	214 (53.6)
No	186 (46.4)
I have sufficient information about HPV and its vaccine to decide whether to receive the vaccine	
Yes	77 (19.2)
No	323 (80.8)
I am sure that the HPV vaccine is highly effective	
Yes	170 (42.5)
No	230 (57.6)
I am sure that the HPV vaccine is safe	
Yes	174 (43.5)
No	226 (56.4)
HPV vaccination can lead to an increase in risky sexual behaviour	
Yes	101 (25.2)
No	299 (74.8)

Acceptability of HPV vaccine among respondents

About 40% of the respondents support HPV vaccine for an adolescent. Half (50.8%) of the respondents want the vaccine to be readily available and are ready to be vaccinated if the vaccine is available. The majority (74.8%) of the respondents wants to be more educated on the vaccine. Major reasons why the respondents will not take the vaccine if readily available were lack of parental permission and have had no sexual exposure (91.3% and 83.8% respectively). Only 2.8% of the respondents have been vaccinated and 41.0% were willing to share the fact that they have been vaccinated with their friends. Overall 74.5% of respondents have high acceptability and 25.5% had low acceptability.

Factors significantly associated with acceptability of Human papilloma virus vaccine include Age ($p < 0.001$), mothers' educational level ($p < 0.001$), knowledge ($p = 0.006$), perceived vaccine efficacy ($p < 0.001$) and perceived fatality of cervical cancer ($p < 0.001$). A higher percentage of respondents with good knowledge (88.9%) have high acceptability for the vaccine compared to 62.7% among those with poor knowledge ($p = 0.006$). A higher proportion of respondents whose mother had secondary education and above (66.9%), and those who perceived HPV vaccine to be effective (87.1%) had high acceptability score for HPV vaccine (Table 4).

The predictors of acceptability of HPV vaccine as determined by logistic regression is as shown in Table 5

The result showed that respondents within the age group 16-21 years were four times more likely to accept HPV vaccination than their younger counterpart (Adjusted odds ratio (AOR) 4.05, CI = 2.30-5.45). Respondents with good knowledge of cervical cancer, HPV and HPV vaccine were three times more likely to accept the vaccine compared to those with poor know-

Table 4. *Acceptability of HPV vaccine among respondents*

Acceptability of HPV vaccine	**Frequency (%)**
Do you support Human Papilloma virus vaccine for adolescent	
Yes	147 (39.7)
No	253 (63.3)
Do you want human papilloma virus vaccine to be readily available	
Yes	203 (50.8)
No	197 (49.2)
Do you want adolescent to be more educated on this vaccine	
Yes	299 (74.8)
No	101 (25.2)
If available, will you accept the vaccine?	
Yes	203 (50.8)
No	197 (49.2)
*** If no why**	
My parents will not allow me to	180 (91.3)
I'm not having sexual intercourse yet	165 (83.8)
I think it is expensive	57 (28.9)
I don't know where to get it	28 (14.2)
I'm afraid of its side effects	45 (22.8)
I don't think I need it	60 (30.5)
Have you been vaccinated with HPV vaccine?	
Yes	11 (2.8)
No	389 (97.2)
Are you willing to share the fact that you have been vaccinated with friends?	
Yes	165 (41.2)
No	235 (58.8)
Acceptability score	
High (≥ 2.5)	298 (74.5)
Low (< 2.5)	102 (25.5)

Table 5. *Predictors of HPV vaccine acceptability among respondents*

Variables	**Category of Variables**	**AOR (95%CI)**	**P-Value**
Age group in years	10-15 yrs (Ref) 16-21 yrs	1 4.05 (2.30– 5.45)	0.001
Knowledge	Poor (Ref) Good	1 2.50 (2.31 – 6.83)	0.010
Mothers level of education	Below secondary (Ref) Secondary and above	1 1.55 (2.62 - 4.58)	0.004
Perceived vaccine efficacy	No (Ref) Yes	1 4.13 (1.49 – 4.19)	0.022
Perceived fatality of cancer	No (Ref) Yes	1 4.13 (1.49 – 4.19)	0.047

ledge (AOR = 2.50, CI = 2.31-6.83). Respondents whose mothers had a secondary and above level of education were two times more likely to accept the vaccine compared to those whose mother had below secondary education (AOR = 1.55, CI = 2.62 - 4.58). Respondents who perceived the vaccine as effective were two times more likely to accept the vaccine compared to those who do not (AOR = 1.57, CI = 0.49 – 3.18). Girls who perceived cervical to be a serious disease were four times more likely to accept the vaccine compared to those who do not (AOR = 4.13, CI = 1.49 – 4.19) (Table 5).

DISCUSSION

To avoid diseases altogether is ideal but this is only possible in a limited number of cases. Immunization which can be achieved by vaccination is one of the currently available interventions aimed at specific protection. In this study, only a few of our respondents have heard about cervical cancer, HPV vaccine, and HPV. Also, the majority of the respondents had poor knowledge of cervical cancer, HPV and HPV vaccine. This finding was in keeping with the findings of previous studies among adolescents in Italy which revealed a low level of awareness on HPV (29.8%) (21) and also a study among upper secondary school students in Sweden which placed awareness level on HPV at 13.5% (22). The finding that the majority of respondents in this study had poor knowledge was in keeping with findings of a study done among secondary school students in Sarawak East Malaysia which revealed that 68.1% of the respondents had poor knowledge of cervical cancer (17). Also, findings of studies done in Nigeria among the general population in Lagos (16) and among medical students in Benin (23) on HPV, cervical cancer and HPV vaccine revealed poor knowledge. Although the good knowledge score obtained in the above-mentioned studies was greater than that of our study this was probably because the study was done among medical students and undergraduates who are supposedly more knowledgeable and more exposed than the secondary school students. The poor knowledge among the students reflects a lack of relevant education and may compromise their awareness on their perceived susceptibility to cervical cancer and HPV infection and the severity of its consequences.

Therefore a lot of effort should be put into health educating this upcoming generation on cervical cancer and how it can be prevented. The main source of information on cervical cancer and the HPV vaccine in this study was majorly internet closely followed by media. This was in keeping with findings of a study done in Sawarak Malaysia which revealed the major source of information as internet (32%) followed by media which was (17%) (17) but our findings were contrary to findings of studies done in Lagos among medical students which revealed major source of information to be school teaching (14). From our study, the majority of the student obtained information from the internet indicating access to internet information. Information obtained from this route is seen by them as trustworthy. Therefore, effort should be made to disseminate more updated and verified information regarding HPV infection, HPV vaccine and cervical cancer through the media and safe websites. Although knowledge of cervical cancer, HPV and HPV vaccine was poor among respondents in this study their attitude towards HPV vaccine was positive. More than three-quarters of the respondents said education on HPV vaccine should be implemented in schools. Half of the respondents said it is preferable to vaccinate men and women with the HPV vaccine. Less than half of the respondents said HPV vaccine is safe and highly effective. Majority of the respondents (80.8% and 74.8%) agreed they don't have sufficient information on HPV. This is in keeping with findings of previous studies (20, 24). The finding in our study could be due to the fact that students are aware of routine immunization in children which is known to prevent childhood illnesses and a such may believe that any new vaccine is important in preventing targeted disease.

Acceptability of HPV was high in this study, although only 2.8% have been vaccinated. Less than half of those who have been vaccinated were willing to share the fact that they have been vaccinated with friends. The high acceptability of the HPV vaccine in this study is similar to findings of previous studies done. A study among Swedish upper secondary school students which revealed a high acceptance of HPV among students although awareness and intention to be vaccinated in the future (22). Also, a study titled Public knowledge and attitudes towards Human Papilloma Virus (HPV) vaccination which placed acceptance of HPV vaccine at 88% among the respondents (25). Logistic regression done in this study revealed that factors that predict acceptability of HPV vaccine to the younger age of respondents, secondary and above level of education among respondents, good knowledge of cervical cancer and HPV vaccine, perceived vaccine efficacy and perceived fatality of cervical cancer. This was in keeping with the findings of other studies done in Hong-Kong among adolescent girls which revealed self-perceived susceptibility, social norm and social influences as factors influencing the acceptability of HPV vaccine (24). A study done in Germany among girls aged 9 to 17 years revealed that girls whose mothers had high education were more likely to have already been vaccinated compared to those whose mothers had basic education (26). Brewer and colleagues

found higher vaccine uptake in girls of parents with a college education compared to a high school education (27). In our study, only 2.8% of the respondents have been vaccinated. Other countries, in contrast to Nigeria, have implemented a nationwide organized, school-based HPV immunization programmes and therefore have direct access to the target population. Australia implemented a school-based programme in 2007 and had achieved vaccine coverage of 64 and 80% for girls by 2009 (28). Scotland National Health Services reported that, after implementing a school-based vaccination programme, 88 % of girls in the second, fifth and sixth years of the secondary school received the first two vaccine doses between 2008 and 2009 (29).

Limitations

Our study includes using self-reported data. It could be argued that very young girls may find it difficult understanding the question relating to cervical cancer HPV and HPV vaccination. However, the girls filled out the questionnaire with the assistant of the research assistant and the questions were simplified with the avoidance of the use of medical terms as much as possible.

Implications for Practice and/or Policy

The HPV vaccine was licensed in Nigeria in 2009 and it has not to be introduced into the National immunization programme or a school-based immunization programme organized. Based on the findings of this study that showed high acceptability of the HPV vaccine, it is therefore important for the HPV vaccine to be introduced to our schools.

CONCLUSION

It is therefore important for health educators, school health specialist to health educate students and teachers in schools through health talk on cervical cancer human papilloma virus and HPV vaccine as the participants in this study desire to know more about the vaccine and also organized programmes on the media that will enlighten the public on the danger of cervical cancer and importance of the HPV vaccine . It is also important to lobby and advocate for the HPV vaccine to be given to school girls who are not sexually active free so as to improve coverage as participants in this study express their desire to want the vaccine to be readily available.

ACKNOWLEDGMENTS

The current authors acknowledge useful contributions from Adesegun O. Fatusi MBChB, FWACP, of the community health department of the Obafemi Awolowo University Teaching Hospitals Complex, in Ile Ife, Osun State, Nigeria for his input regarding this article.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Sažetak

PREDIKTORI I PRIHVATANjE HPV VAKCINE MEĐU STARIJIM UČENICAMA SREDNJIH ŠKOLA U ILE-IFEu

Fehintola O Funmito,[1] Fehintola O Akintunde,[2] Ogundele A Olorunfemi,[3] Adegbenro A Caleb,[1] Olowookere A Samuel,[1] Afolabi T Olusegun[1]

[1] Department of Community Health Obafemi Awolowo University, Ile-Ife, Nigeria
[2] Department of Obstretrics and Gyneacology Department Obafemi Awolowo University, Ile-Ife, Nigeria
[3] Department of Community Health and Primary Care, State Specialist Hospital, Ondo City, Nigeria

Uvod: Karcinom cerviksa je drugi po učestalosti tumor kod žena širom sveta i Nigeriji. Smatra se da je humani papiloma virus (HPV) jedan od vodećih uzroka za izazivanje karcinoma grlića materice. Činjenica da HPV vakcinacija može da spreči pojavu ovog smrtnosnog raka je već neko vreme ustanovljena. Iako su vakcine licencirane u Nigeriji od 2008. godine i dostupne širom sveta, ona još uvek nije uvedena u kalendar obavezne imunizacije u Nigeriji. Ova studija ima za cilj da ispita prediktore i prihvatanje HPV vakcine među starijim učenicama srednjih škola u Ile-Ifeu.

Metod: Ova deskriptivna studija uvrstila je 400 ispitanika, nasumično izabranih iz različitih srednjih škola u centralnoj regiji Ile Ife-a. Podaci su dobijeni korišćenjem upitnika, koji je imao za cilj da ispita nivo znanja, stavove i prihvatanje karcinoma grlića materice, humanog papiloma virusa, kao i HPV vakcine. Podaci su analizirani korišćenjem deskriptivne i inferentne statistike.

Rezultati: Najveći broj ispitanika (93,2%) imao je jako nizak stepen znanja o karcinomu grlića materice, HPV i HPV vakcini. Stavovi prema karcinomu grlića materice i HPV vakcini su bili veoma dobri, s tim da je 74,5% imalo izuzetno visok stepen prihvatanja HPV vakcine. Samo 2,8% ispitanika je bilo vakinisano. Prediktori prihvatanja HPV vakcine su bili: mlađa uzrasna grupa ((AOR) 4,05, CI = 2,30-5,45), dosta dobro znanje iz ove oblasti ((AOR = 2,50, CI = 2,31 - 6,83), viši stepen obrazovanja majke ((AOR = 1,55, CI = 2,62 - 4,58), shvatanje stope smrtnosti kod osoba obolelih od karcinoma grlića materice (AOR = 4,13, CI = 1,49 - 4,19) i razumevanje efikasnoti HPV vakcine (AOR = 1,57, CI = 0,49 – 3,18).

Zaključak: Nivo znanja starijih učenica srednjih škola o karcinomu grlića materice, HPV i HPV vakcini je izuzetno nizak, iako je prihvatanje HPV vakcine izuzetno visoko. Visoki stepen prihvatanja vakcina u ovoj studiji je odraz želje i spremnosti grupe u riziku, da uči više o ovoj temi. Postoji jaka potreba da se naprave zdravstveni programi u školama, koji će se fokusirati na zdravstvenu edukaciju učenika, kako bi se sprečio razvoj ovog preventabilnog karcinoma i kako bi se obezbedio veći broj vakcina. Uključenje HPV vakcine u Nacionalni program obavezne imunizacije u Nigeriji može izuzetno da podigne nivo svesti o karcinomu grlića matericei i prihvatanju vakcina.

Ključne reči: znanje, prihvatanje, HPV vakcine, starije učenice srednjih škola.

REFERENCES

1. Bruni L, Barrionuevo-Rosas L, Albero G, Aldea M, Serrano B, Valencia S, et al. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human papilloma virus and related diseases inIndia Summary Report. 2015: 12-23.

2. Keam SJ, Harper DM. Human papillomavirus types 16 and 18 vaccine (recombinant, AS04 adjuvanted adsorbed) [Cervarix™]. Drugs. 2008; 68(3): 359-72.

3. Olowookere S, Abioye-Kuteyi E, Airewele E, Fasure H, Fayose O, Onakpoma F, et al. Awareness and uptake of human papilloma virus vaccination and cervical cancer screening among female undergraduate students in a tertiary institution in Nigeria. Nigerian Journal of Family Practice. 2012; 3(1): 27-32.

4. MuZoz N, Franco EL, Herrero R, Andrus JK, de Quadros C, Goldie SJ, et al. Recommendations for cervical cancer prevention in Latin America and the Caribbean. Vaccine. 2008; 26 (suppl 11): L96-107.

5. Dunne EF, Unger ER, Sternberg M, McQuillan G, Swan DC, Patel SS, et al. Prevalence of HPV infection among females in the United States. Jama. 2007; 297(8): 813-9.

6. Harper DM, Franco EL, Wheeler CM, Moscicki A-B, Romanowski B, Roteli-Martins CM, et al. Sustained efficacy up to 4 · 5 years of a bivalent L1 virus-like particle vaccine against human papilloma virus types 16 and 18: follow-up from a randomised control trial. The Lancet. 2006; 367(9518): 1247-55.

7. Markowitz LE, Dunne E, Saraiya M, Lawson H, Chesson H, Unger E. Quadrivalent human papillomavirus vaccine. Morbidity and Mortality weekly report. 2007; 56(RR-2): 1-24.

8. Mc Cormack PL, Joura EA. Quadrivalent Human Papilloma virus (Types 6, 11, 16, 18) Recombinant Vaccine (Gardasil®). Drugs. 2010; 70(18): 2449-74.

9. Monie A, Hung C-F, Roden R, Wu TC. Cervari: a vaccine for the prevention of HPV 16, 18- associated cervical cancer. Biologics. 2008; 2(1): 97-105.

10. Mogensen O. Improvement of women's health–HPV vaccination after 16 years of age?: Taylor & Francis; 2009.

11. Erickson BK, Alvarez RD, Huh WK. Human papillomavirus: what every provider should know. Am J Obstet Gynecol. 2013; 208(3): 169-75.

12. Agida TE, Akaba GO, Isah AY, Ekele B. Knowledge and perception of human papilloma virus vaccine among the antenatal women in a Nigerian tertiary hospital. Niger Med J. 2015; 56(1): 23-7.

13. Patel MS, Kakkad KM, Patel SV. Human papilloma virus vaccination: recent trends in prevalence and recommendations in India. Journal of SAFOMS. 2014; 2(1): 26.

14. Adejuyigbe FF, Balogun M, Sekoni AO, Adegbola AA. Cervical cancer and human papilloma virus knowledge and acceptance of vaccination among medical students in Southwest Nigeria. African Journal of Reproductive Health. 2015; 19 (1): 140-8: erratum. African journal of reproductive health. 2015; 19(2): 139.

15. Chiang VCL, Wong HT, Yeung PCA, Choi YK, Fok MSY, Mak OI, et al. Attitude, acceptability and knowledge of HPV vaccination among local university students in Hong Kong. Int J Environ Res Public Health. 2016; 13(5): E486.

16. Ezenwa BN, Balogun MR, Okafor IP. Mothers' human papilloma virus knowledge and willingness to vaccinate their adolescent daughters in Lagos, Nigeria. Int J Womens Health. 2013; 5: 371-7.

17. Rashwan H, Lubis SH, Ni KA. Knowledge of cervical cancer and acceptance of HPV vaccination among secondary school students in Sarawak, Malaysia. Asian Pac J Cancer Prev. 2011; 12(7): 1837-41.

18. Agius PA, Pitts MK, Smith AM, Mitchell A. Human papillomavirus and cervical cancer: Gardasil vaccination status and knowledge amongst a nationally representative sample of Australian secondary school students. Vaccine. 2010; 28(27): 4416-22.

19. Araoye MO. Research methodology with statistics for health and social sciences. 1st Ed. Ilorin: Nathadex Publisher. 2004: 25-120.

20. Jalani FFM, Rani MDM, Isahak I, Aris MSM, Roslan N. Knowledge, attitude and practice of human papilloma virus (HPV) vaccination among secondary school students in rural areas of Negeri Sembilan, Malaysia. International Journal of Collaborative Research on Internal Medicine & Public Health. 2016; 8(6); 420-34.

21. Di Giuseppe G, Abbate R, Liguori G, Albano L, Angelillo I. Human papillomavirus and vaccination: knowledge, attitudes, and behavioural intention in adolescents and young women in Italy. BJC. 2008; 99(2): 225-9.

22. Gottvall M, Larsson M, Höglund AT, Tydén T. High HPV vaccine acceptance despite low awareness among Swedish upper secondary school students. European J Contracept Reprod Health Care. 2009; 14(6): 399-405.

23. Onowhakpor A, Omuemu V, Osagie O, Odili C. Human Papilloma Virus vaccination: knowledge, attitude and uptake among female medical and dental students in a tertiary institution in Benin-City, Nigeria. Journal of Community Medicine and Primary Health Care. 2016; 28(2): 101-8.

24. Lee A, Ho M, Cheung CKM, Keung VMW. Factors influencing adolescent girls' decision in initiation for human papillomavirus vaccination: a cross-sectional study in Hong Kong. BMC public health. 2014; 14(1): 925.

25. Walsh CD, Gera A, Shah M, Sharma A, Powell JE, Wilson S. Public knowledge and attitudes towards Human Papilloma Virus (HPV) vaccination. BMC public health. 2008; 8(1): 368.

26. Schülein S, Taylor KJ, König J, Claus M, Blettner M, Klug SJ. Factors influencing uptake of HPV vaccination among girls in Germany. BMC public health. 2016; 16(1): 995.

27. Brewer NT, Gottlieb SL, Reiter PL, McRee A-L, Liddon N, Markowitz L, et al. Longitudinal predictors of HPV vaccine initiation among adolescent girls in a high-risk geographic area. Sex Transm Dis. 2011; 38(3): 197-204.

28. Markowitz LE, Tsu V, Deeks SL, Cubie H, Wang SA, Vicari AS, et al. Human papillomavirus vaccine introduction–the first five years. Vaccine. 2012; 30: F139-48.

29. Potts A, Sinka K, Love J, Gordon R, McLean S, Malcolm W, et al. High uptake of HPV immunisation in Scotland–perspectives on maximising uptake. Euro Surveill. 2013; 18(39): 1-10.

Correspondence to/Autor za korespondenciju
Funmito Omolola Fehintola
Department of Community Health Obafemi Awolowo University Ile-Ife, Nigeria
E-mail Address : funmitoabioye@yahoo.com
Phone number: 2348033913964, Nigeria

SANAMED
2019; 14(2): 163–167
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i2.308
UDK: 617.741-004.1-089:616.61-78-056.24
ID: 278329612
Original article

INCIDENCE OF POSTERIOR CAPSULAR OPACIFICATION AFTER UNEVENTFUL CATARACT SURGERY IN PATIENTS ON HEMODIALYSIS

Yildiz Aydin, Comez Taskiran Arzu

[1] Canakkale Onsekiz Mart University, Faculty of Medicine, Department of Ophthalmology, Turkey

Primljen/Received 22. 01. 2019. god. Prihvaćen/Accepted 08. 06. 2019. god.

Abstract: **Purpose:** To evaluate the incidence of posterior capsular opacification after cataract surgery in patients on hemodialysis. Patients and Methods: Fifty patients on hemodialysis undergoing cataract surgery and 50 patients undergoing cataract surgery in a similar age group without any systemic disease were compared retrospectively. All patients underwent uneventful phacoemulsification surgery. Hydrophilic monoblock, sharp-edged acrylic intraocular lens (Spectrafold™, Gujarat, India) was used. A complete ophthalmological examination was performed on the patients who were evaluated at the postoperative 12th month follow-up examination. Posterior capsular opacification was evaluated by the retroillumination method. According to the reflection from retroillumination, cases with posterior capsular opacification were divided into three groups as mild, moderate and severe.

Results: Age groups and male to female ratios were similar. Mean best corrected visual acuity (BCVA) was 0.23 in the hemodialysis group and 0.22 in the control group, preoperatively. At the end of the first year, the mean BCVA was 0.88 in the hemodialysis group and 0.94 in the control group. In the hemodialysis group, the percentage of posterior capsular opacification was 60% and was 14% in the control group; this difference was statistically significant ($p < 0.05$). While the capsular opacity was mild in all 7 patients in the control group, it was mild in 19 patients, moderate in 8 and severe in 3 patients in the hemodialysis group. **Conclusion:** The incidence of posterior capsular opacification after uneventful cataract surgery is found to be higher in patients on hemodialysis than in the normal population.

Key words: Hemodialysis, cataract, phacoemulsification, posterior capsular opacity, PCO.

INTRODUCTION

Cataract is one of the most common causes of loss of vision in the elderly population. Currently, the method used for surgery is the phacoemulsification surgery. With this method, lens material is emulsified and aartificial intraocular lens (IOL) is inserted in the bag formed by lens capsule.

The most common complication encountered after uneventful phacoemulsification surgery is proliferation of the remaining lens epithelial cells within the capsule transforming to a fibrotic process leading to posterior capsule opacification (PCO). The incidence of PCO is between 2 to 5% in the literature, though rates up to 50% are also reported (1-5). Yag laser capsulotomy is performed as treatment.

The causes of posterior capsular opacification may be listed as factors linked to the surgery, the type and design of the IOL inserted and the factors related to the patient. During surgery, if lens cells are not sufficiently cleaned from the posterior capsule, PCO may easily develop. In order to prevent PCO, it is recommended that an extra cleaning attempt like polishing should be applied routinely to the posterior capsule (3).

The type, material and design of IOL also affect PCO development. The PCO rates were common with IOLs made of polymethyl methacrylate (PMMA), but there has been a large reduction in PCO incidence with acrylic IOLswhich are recently more commonly used.Studies in recent years have shown that use of sharp-edged acrylic IOL reduces the development incidence of PCO (2, 4, 5).

The patient-linked factors are young patient age,patient with systemic disease such as diabetes,, patients with ocular disease such as uveitis and medication use such as corticosteroids (6). PCO is commonly observed in those with pseudoexfoliation, uveitis or traumatic cataracts and patients with myotonic dystrophy (7).

The correlation between PCO with systemic diseases has not been fully researched, apart from diabetes. Cataracts are commonly observed with medications

used for chronic renal failure and with the effect of hemodialysis (8). This study was planned as no study related to the development of opacification of the posterior capsule after cataract surgery in hemodialysis patients was found in the literature.

PATIENTS AND METHODS

This study was completed by retrospectively screening of files of hemodialysis patients who underwent uneventful phacoemulsification surgery from 2015 to 2017. Informed consent was obtained from all patients and the study abided by the Declaration of Helsinki criteria. Ethical approval was taken from Canakkale Onsekiz Mart University Ethical Committe. Fifty patients undergoing hemodialysis with cataract surgery were compared with 50 healthy patients without systemic disease in a similar age group.

Inclusion criteria for the study are as follows: adult patients aged 50 years and older, those with no systemic disease, those under hemodialysis treatment and those attending 1-year follow-up. Patients with uveitic cataracts, with corneal pathology or with retinal disease were not included in the study. Visual acuity was assessed with Snellen test.

For the surgical method, after 2.8 mm corneal incision intracameral lidocain Hcl and viscoelastic are administered, 5-5.5 mm capsulorhexis was performed. All surgeries were performed by one surgeon. (AY) Lens material was aspirated with a phaco instrument (Infiniti Vision system, Alcon Laboratories, Inc., Fort Worth, TX, USA). A 0.9 mm Kelman Micro Tipphaco tip with 45° was used in all cases. Cortex material was cleaned with irrigation aspiration.Hydrophilic acrylic IOL (Spectrafold™, Gujarat, India) was used. Intraocular lens properties were refractive index 1.465, water content 26%, monoblock, sharp-edges, non-ionic structure with material stated to reduce PCO rates. All patients were prescribed with topical corticosteroid (Maxidex, Alcon Laboratories) and antibiotic (Vigamox, Alcon Laboratories) drops five times daily for three weeks.

Patients attending the 1st year follow-up examination had full ophthalmologic examination performed and PCO development was assessed with the retroillumination method by biomicroscopy. According to reflections from retroillumination, PCO was classified in three groups as mild, moderate and severe. After pupillary dilatation, peripheral capsular opacification was accepted as mild, PCO extending to paracentral area as moderate, and PCO including center of the lens is accepted as severe.

Statistical analyses were evaluated withStatistical Package for the Social Sciences (SPSS) program. Categorical variables were given as mean ± standard deviations and with percentages. For the comparison of the groups independentsamples t-test was used. Statistical significance was accepted as a p value of < 0.05.

RESULTS

Mean age in the hemodialysis group was 65.2 years, while it was 66.7 years in the control groups ($p > 0.05$). The female/male ratio in the hemodialysis group was 24/26, while it was 21/29 in the control group.

Average phacoemulsification time and surgery duration were 8.2% and 13.4 minutes in hemodialysis group, respectively. Phaco-power were used as with a range of 30 to 40 according to the grade of cataract. Average phaco-time and surgery duration were 8.1% and 13.1 minutes in control group. There was no statistical significance in terms of phaco time and surgery duration ($p > 0.05$).

Preoperative mean best corrected visual acuity was 0.23 in the hemodialysis group, while it was 0.22 in the control group. At the end of the first year, mean visual acuity was 0.88 in the hemodialysis group and 0.94 in the control group. Details related to upper and lower values are given in Table 1.

The most noteworthy finding was the PCO incidence in the hemodialysis group. Rates of 60% were

Table 1. *Demographic and Visual Acuity findings*

	Hemodialysis Group	**Control Group**	**P value**
Age	65.2 ± 3.4 Min-max: 58-73	66.7 Min-max: 61-77	0.447
Gender (Female/Male)	24 / 26	21 / 29	0.549
Mean Preoperative best corrected visual acuity (Snellen Chart)	0.23 Min-max: 0.1-0.4	0.22 Min-max: 0.1-0.4	0.689
Mean Postoperative 3rd month best corrected visual acuity (Snellen Chart)	0.97	0.96	0.041
Mean Postoperative 1st year best corrected visual acuity (Snellen Chart)	0.88	0.94	0.000
Posterior Capsular Opacification Rate	60%	14%	0.000

Table 2. *Ocular characteristics*

	Hemodialysis Group	**Control group**
Types of Cataract	Cortical - 13 Nuclear - 12 Posterior subcapsular – 17 Mature - 8	Cortical - 10 Nuclear - 14 Posterior subcapsular-12 Mature -14

observed in the hemodialysis group while a rate of 14% is seen in the control group and this difference was statistically significant ($p < 0.05$). All 7 patients with PCO in the control group had mild degree of capsular opacity, while in the hemodialysis group 19 patients had mild, 8 patients had moderate and 3 patients had severe degrees of opacity identified.

Ocular characteristics were listed in Table 2.

DISCUSSION

There are variety of studies related to ocular findings in patients undergoing hemodialysis in the literature. One of these is the study by Minen et al. about intraocular pressure, corneal thickness, eye dryness and contrast sensitivity in 42 hemodialysis patients. While there was no difference in terms of intraocular pressure and corneal thickness compared to the control group, the hemodialysis group had lower Schirmer test results and lower contrast sensitivity degrees (9). A study of 30 patients by Demir et al. identified cataract in 3 patients, while 22 patients had corneal-conjunctival calcification (10).

One of the eye findings due to high urea levels and calcification in hemodialysis patients, is cataracts withrates up to 58% (11, 12, 13). A study of patients with chronic renal failure reported a strong correlation between the severity of renal disorder and cataract development risk. (14).

Dursun et al. performed extracapsular cataract extraction surgery with small incision and suture methods for 82 chronic renal failure patients with cataracts in a two-year period. Of the patients, 14.6% (12 patients) encountered a variety of postoperative problems. In 10 of these 12 patients, suture infection was observed (15).

With cataract surgery with the narrow incision entry method and phacoemulsification surgery, almost no sutures are used and more successful results are obtained. A study by Chen et al. reported 1.0 level of visual acuity was reached in 52% of patients in the postoperative period (16). In our study, 72% of patients had 1.0 level of visual acuity identified in the first postoperative month.

Though there are studies related to hemodialysis and cataracts in the literature, there was no study encountered about the incidence of posterior capsular opacification in hemodialysis patients. This topic was studied in our research and high rates of PCO incidence were observed. The reasons for this may be listed as lens epithelial cells remaining during surgery preparing the way for formation of posterior capsule opacification. These cells are present in nearly all patients at low amounts, but are known to remain at the lens equator.

During cataract surgery, the anterior capsule of the lens is opened and there is direct contact between anterior chamber fluid and lens contents. As hemodialysis patients have more accumulation of toxic metabolites compared to normal individuals, the contact rate of urea to the lens increases and PCO may be observed more often due to increased oxidative stress (10,17). Another probable explanation is that as the posterior subcapsular region is sensitive to oxidative stress, this may also be valid for the posterior capsule (18).

Additionally, abnormalities of remaining lens epithelial cells due to acidosis (19) or disrupted lens epithelial cell metabolism linked to vitamin D deficiency resulting in formation of calcium deposits in the posterior capsule, may be the reason for the high incidence of PCO observed (20).

In conclusion, hemodialysis patients with uneventful cataract surgery appear to have higher incidence of posterior capsule opacification compared to the normal population.

Abbreviations

PCO — posterior capsular opacification
IOL — intraocular lens
PMMA — polymethyl methacrylate
SPSS — Statistical Package for the Social Sciences

Acknowledgment: None

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Licensing

Sažetak

UČESTALOST ZAMUĆENJA ZADNJE KAPSULE SOČIVA NAKON RUTINSKE OPERACIJE KATARAKTE KOD PACIJENATA NA HEMODIJALIZI

Yildiz Aydin, Comez Taskiran Arzu

[1] Canakkale Onsekiz Mart University, Faculty of Medicine, Department of Ophthalmology, Turkey

Cilj: Cilj ovog rada bio je da se proceni incidenca zamućenja zadnje kapsule sočiva nakon operacije katarakte kod pacijenata na hemodijalizi.

Pacijenti i metode: 50 pacijenata na hemodijalizi koji su bili podvrgnuti operaciji katarakte i 50 pacijenata slične starosne dobi i bez sistemskih oboljenja koji su bili podvrgnuti operaciji katarakte su upoređivani retrospektivno. Svi pacijenti su bili podvrgnuti rutinskoj fakoemulzifikaciji. Korišćena su hidrofilna monoblok, intraokularna sočiva oštrih ivica (Spectrafold™, Gujarat, Indija). Kompletan oftalmološki pregled izveden je kod svih pacijenata 12og postoperativnog meseca na redovnom kontrolnom pregledu. Zamućenja zadnje kapsule sočiva ispitivano je metodom retroiluminacije. Prema refleksiji dobijenoj retroiluminacijom, slučajevi sa zamućenjem zadnje kapsule sočiva bili su podeljeni u tri grupe: kao blago, umereno i ozbiljno zamućenje.

Rezultati: Odnosi po pitanju godina starosti i pola unutar grupa bili su slični. Srednja najbolje korigovana vidna oštrina (BCVA) bila je 0,23 u grupi pacijenata na hemodijalizi i 0,22 u kontrolnoj grupi, preoperativno. Na kraju prve godine, srednja vrednost BCVA bila je 0,88 u grupi na hemodijalizi i 0,94 u kontrolnoj grupi. U grupi na hemodijalizi procenat zamućenja kapsule bio je 60%, dok je u kontrolnoj grupi iznosio 14%. Ova razlika je bila statistički značajna ($p < 0,05$). Dok je kapsularno zamućenje bilo blago kod svih 7 pacijenata u kontrolnoj grupi, bilo je blago kod 19 pacijenata, umereno kod 8 i teško kod 3 pacijenta u grupi koji su bili na hemodijalizi.

Zaključak: Pokazalo se da je učestalost zamućenja zadnje kapsule sočiva nakon rutinske operacije katarakte veća kod pacijenata na hemodijalizi nego u normalnoj populaciji.

Ključne reči: hemodijaliza, katarakta, fakoemulzifikacija, zamućenje zadnje kapsule sočiva, PCO.

REFERENCES

1. Wilhelmus KR, Emery JM. Posterior capsule opacification following phacoemulsification. Ophthalmic Surg. 1980; 11(4): 264-7.

2. Wu S, Tong N, Pan L, Jiang X, Li Y, Guo M, et al.. Retrospective analyses of potential risk factors for posterior capsule opacification after cataract surgery. J Ophthalmol. 2018; 2018:9089285. doi: 10.1155/2018/9089285.

3. Awasthi N, Guo S, Wagner BJ. Posterior capsular opacification: a problem reduced but not yet eradicated. Arch. Ophthalmol. 2009; 127(4): 555-62.

4. Çomez AT, Ozkurt YB, Karadag O, Dogan OK. The effect of intraocular lens material on posterior capsular opacification. Kartal Egitim ve Arastirma Hastanesi Tip Dergisi. 2006; 17(1): 17-21.

5. Zhao Y, Yang K, Li J, Huang Y, Zhu S. Comparison of hydrophobic and hydrophilic intraocular lens in preventing posterior capsule opacification after cataract surgery: An updated meta-analysis. Medicine (Baltimore). 2017; 96(44): e8301. doi:10.1097/MD. 0000000000008301.

6. Iliescu IM, Constantin MA, Cozma C, Moraru OM, Moraru CM. Posterior capsule opacification and Nd-YAG rates evaluation in a large series of pseudophakic cases. Rom J Ophthalmol. 2017; 61(4): 267–74.

7. Langwiñska-Woœko E, Broniek-Kowalik K, Szulborski K. The impact of capsulorhexis diameter, localization and shape on posterior capsule opacification. Med Sci Monit. 2011; 17(10): CR577-82.

8. Rim TH, Yoon CY, Park HW, Chung EJ: Association between starting hemodialysis for end-stage renal disease and incident cataract surgery: a 12-year nationwide cohort study. Invest Ophthalmol Vis Sci. 2016; 57(3): 1112–9.

9. Minen M, Ar2c2 MK, Erdogan H, Topalkara A, Toker İ, Gültekin F. ŠOphtalmologic findings in hemodialysis patients[1]. Turk J Ophthalmol 2001; 31: 352-60.

10. Demir MN, Kocaoglan H, Akay H, Duranay M, Duman S. [Ophtalmologic findings in chronic renal disease]. Turk J Ophthalmol 2006; 36(2): 150-5.

11. Stibor V, Lachmanová J, Tomásek R. Changes in the lens and cataract surgery in dialyzed patients. Cesk Oftalmol. 1989; 45(4): 253-60.

12. Vrabec R, Vatavuk Z, Pavlovic D, Sesar A, Cala S, Mandic K, et al. Ocular findings in patients with chronic renal failure undergoing hemodialysis. Coll Antropol. 2005; 29(suppl 1): 95-8.

13. Albert K, Sennesael J, Haentjens P. Incidence and risk factors for posttransplant subcapsular cataract: a long-term retrospective cohort study. Transplant Proc. 2011; 43(9): 3465-9.

14. Liu YT, Hung TY, Lee YK, Huang MY, Hsu CY, Su YC. Association between chronic kidney disease and risk of cataract: A nationwide retrospective cohort study. Am J Nephrol. 2017; 45(6): 524-31.

15. Dursun D, Akova YA, Akman A, Oto S, Aydin P. Complications of extracapsular cataract surgery in chronic renal failure patients. Eye (Lond). 2000; 14 (2): 176-9.

16. Chen Y, Cai J, Liu H. Phacoemulsification and intraocular lens implantation in patients with chronic renal failure and cataract. Zhonghua Yan KeZaZhi. 2001; 37(5): 332-4.

17. Delcourt C, Carriere I, Delage M, Descomps B, Cristol JP, Papoz L. Associations of cataract with antioxidant enzymes and other risk factors: the French Age-Related Eye Diseases (POLA) Prospective Study. Ophthalmology. 2003; 110(12): 2318–26.

18. Hodge WG, Whitcher JP, Satariano W. Risk factors for age related cataracts. Epidemiol Rev. 1995; 17(2): 336–46.

19. Metcalfe W, Khan IH, Prescott GJ, Simpson K, Macleod AM; Scottish Renal Registry. End-stage renal disease in Scotland: outcomes and standards of care. Kidney Int. 2003; 64(5): 1808–16.

20. Huynh SC, Kifley A, Strippoli GF, Mitchell P. Is renal impairment a predictor of the incidence of cataract or cataract surgery: findings from a population-based study. Ophthalmology. 2005; 112(2): 293–300.

Correspondence to/Autor za korespondenciju
Dr. Aydin YILDIZ
Address: Canakkale Onsekiz Mart University, Faculty of Medicine,
Department of Ophthalmology Barbaros Cad, 17100, Canakkale -TURKEY
Telephone: +9 0533 5594850
Fax: 0212 6954829
E-mail: aydinyildiz@comu.edu.tr

SANAMED
2019; 14(2): 169–174
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i2.331
UDK: 616.33/.35-005.1-074
ID: 278322188
Original article

RED CELL DISTRIBUTION WIDTH AND PLATELET INDICES AS PREDICTORS IN DETERMINING THE PROGNOSIS OF UPPER GASTROINTESTINAL SYSTEM BLEEDING

Abaylı Bahri,[1] Gencdal Genco[2]

[1] Cukurova Dr. Askım Tufekci Hospital, Department of Gastroenterology and Hepatology, Adana, Turkey
[2] Istanbul Atasehir Memorial Hospital, Department of Gastroenterology, Istanbul, Turkey

Primljen/Received 17. 04. 2019. god. Prihvaćen/Accepted 17. 06. 2019. god.

Abstract: **Background and Aim:** Acute upper gastrointestinal bleeding (AUGIB) is one of the most common medical emergencies. Early detection of at-risk patients is beneficial with respect to treatment and prognosis. We investigated whether severity of ulcers were associated with red blood cell distribution width (RDW), plateletcrit (PCT), mean platelet volume (MPV) and platelet distribution width (PDW). **Materials and Methods:** All patients presenting to the emergency department with AUGIB between January 2014 and December 2017 were included in the study. Endoscopy reports, complete blood counts, patient demographic characteristics, and endoscopy results were obtained retrospectively from hospital records. Patients with grade I or grade II ulcers (based on the Forrest classification) were compared in regard to these parameters. **Results:** In total, 373 male and 211 female patients with a mean age ± SD of 66.36 ± 17.36 were included in this study. Ulcers were detected in 396 of 584 patients (67.8%). There were no differences with respect to RDW or platelet indices between groups.

Conclusions: Patients presenting with AUGIB should receive rapid diagnosis and treatment. In this study of patients with AUGIB grouped by bleeding aetiology, probable early prognostic parameters were not associated with bleeding severity among patients diagnosed with gastric or duodenal ulcers.

Key words: Endoscopy, gastrointestinal bleeding, ulcer, RDW, PCT, MPV, PDW.

INTRODUCTION

Acute upper gastrointestinal bleeding (AUGIB) usually manifests itself with hematemesis, melena, or both. Most cases of AUGIB resolve spontaneously (70%–80%) and mortality is low (3%–6%). However, patients should be rapidly diagnosed and treated. Erythrocyte detection in nasogastric lavage at admission, tachycardia, and haemoglobin level less than 8 g/dl indicate severe AUGIB. Early detection of high-risk patients affects prognosis and treatment and is cost-effective (1-7).

Red cell distribution width (RDW), a measure of the variability in size of circulating erythrocytes, is used routinely in clinical practice to determine anaemia subtype. Studies also suggest that RDW predicts morbidity and mortality for various severe diseases. Furthermore, RDW may independently predict development of massive and recurrent bleeding in patients experiencing percutaneous coronary intervention, intracranial hematoma, or multiple traumas. Plateletcrit (PCT), mean platelet volume (MPV), and platelet distribution width (PDW) are routinely evaluated as part of the complete blood count. It has been suggested that these parameters may be useful in understanding inflammatory, ischemic, and thrombotic conditions as well. To date, the number of studies addressing the relationship between gastrointestinal diseases and platelet indices is low. A few studies have shown MPV to be low during acute exacerbations ofinflammatory bowel disease and MPV to be high among patients with colon cancer and a poor prognosis. Upper gastrointestinal endoscopy (UGE), which is usually required to diagnose and manage AUGIB in the hospital, plays an important role in determining AUGIB severity and aetiology. In patients with haemorrhage, a wide variety of endoscopic methods (eg, endoscopic sclerotherapy and endoscopic haemoclipping) are commonly used. The Forrest classification, which is commonly used in conjunction with UGE to describe peptic ulcers, isvery useful in determining re-bleeding risk; however, UGE is not

performed routinely at all health centres. Patients presenting with severe AUGIB should be selected carefully for prompt transfer to centres with endoscopy capabilities (8-14).

In this study, our primary aim was to describe AUGIB aetiology for patients presenting to our hospital. Secondarily, we aimed to determine whether AUGIB severity (Forrest classification) was related to RDW, PCT, MPV, and PDW.

MATERIALS AND METHODS

Patient data and endoscopy reports were retrospectively obtained from hospital records. Between January 2014 and December 2017, patients who were presented to our emergency department with AUGIB and underwent upper gastrointestinal endoscopy were eligible for the inclusion in the study. Patients were excluded if they had a history of haematologic disease, refused laboratory testing or treatment, requested transfer to another facility, were pregnant, or had medical records that lacked clinical or laboratory data. Approval from local ethics committee and written/informed consent from patients were not obtained because the study was retrospective. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Endoscopy reports for patients with confirmed gastric or duodenal ulcers were classified by a gastroenterologist according to the Forrest classification: 1a and 1b ulcers were classified as high re-bleeding risk; 2a, 2b and 2c ulcers were classified as increased re-bleeding risk. Patients were divided into 4 groups according to RDW:(1) RDW less than 12.8; (2) RDW greater than 12.9 and less than 14.4; (3) RDW greater than 14.5 and less than 16.5; or (4) RDW greater than 16.6.

Complete blood count values and demographic characteristics were retrospectively obtained from hospital records. Patients with high re-bleeding risk (Forrest 1) and increased re-bleeding risk (Forrest 2) were compared to each other.

RESULTS

Demographic characteristics and endoscopy results for 584 patients (63.9% male) were included in this study. The mean ± SD age was 66.36 ± 17.36 years. Demographic characteristics and endoscopy results are presented in Table 1 and Figure 1. Duodenal and gastric ulcers were the most common and second most common causes of upper gastrointestinal bleeding, respectively.

Gastric and duodenal ulcers were detected in 396 of 584 patients. According to the Forrest classification for ulcers, 61 (15.4%) had type Ia; 73 (18.5%) had Ib; 184 (46.5%) had IIa; 72 (18.1%) had IIb and 6 (1.5%) had IIc.

Table 1. *Demographics of the patients*

Age, mean (SD)	**66.36 (17.63)**
Male, n (%)	373 (63.9)
Medication, n (%)	58 (9.9)
Antiplatelets	43 (7.3)
NSAIDs	8 (1.4)
Anticoagulants	7 (1.2)
Melena, n (%)	220 (37.7)
Syncope, n (%)	359 (61.5)
CLD, n (%)	48 (8.2)
Cause of UGIB	
Duodenal Ulcer, n (%)	256 (43.8)
Gastric ulcer, n (%)	140 (24)
Esophageal varices, n (%)	55 (9.4)
Esophageal ulcer, n (%)	53 (9.1)
Erosive gastritis ,n (%)	21 (3.6)
Malignancy, n (%)	19 (3.3)
Others, n (%)	40 (6.8)
Hemoglobin, mean (SD) (g/dl)	9.35 (2.3)
Hematocrites (%)	28.4 (6.7)
Platelets (10^9)	234 (95)
MPV (fl)	9.5 (1.8)
PCT	0.22 (0.09)
PDW (fl)	13.8 (3.3)
RDW (%)	15.5 (2.7)
1 (RDW < 12.8)	48 (8.2)
2 (RDW 12.9 – 14.4)	189 (32.4)
3 (RDW 14.5 – 16.5)	195 (33.4)
4 (RDW > 16.5)	152 (26)
Forrest Classification (n: 396)	
Ia, n (%)	61 (15.4)
Ib, n (%)	73 (18.5)
IIa, n (%)	184 (46.5)
IIb, n (%)	72 (18.1)
IIc, n (%)	6 (1.5)

SD: Standard deviation, n: number, NSAID: Non-steroid anti-inflammatory drugs, CLD: Chronic liver disease, UGIB: Upper gastrointestinal bleeding, MPV: Mean platelet volüme, PCT: Platecrite, PDW: Platelet distrubution width, RDW: Reticulocytes distrubution width

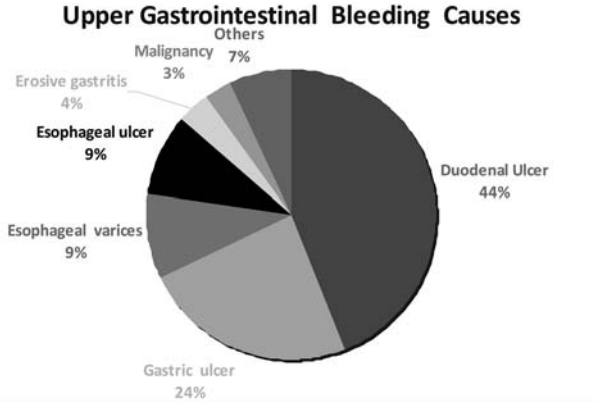


Figure 1

Table 2. *Comparisons of whole blood test parameters between Forrest 1 and Forrest 2 patients*

	Forrest I	**Forrest II**	**P value**
Age	67.7 (18)	63.5 (18)	NS
Hemoglobin, mean (SD) (g/dl)	9.37 (2.5)	9.21 (2.28)	NS
Hematocrites, mean (SD) (%)	28.4 (7.4)	27.9 (6.6)	NS
Platelets, mean (SD) (10^9)	235 (79)	243 (84)	NS
MPV, mean (SD) (fl)	9.5 (1.6)	9.5 (1.8)	NS
PCT, mean (SD)	0.23 (0.1)	0.23 (0.08)	NS
PDW, mean (SD) (fl)	13.5 (3.5)	13.9 (3)	NS
RDW, mean (SD)	15.3 (3.3)	15.2 (2.5)	NS
1 (RDW < 12.8), n (%)	14 (10.4)	23 (8.8)	NS
2 (RDW 12.9 – 14.4), n (%)	52 (38.8)	98 (37.4)	NS
3 (RDW 14.5 – 16.5), n (%)	44 (32.8)	83 (31.7)	NS
4 (RDW > 16.5), n (%)	24 (17.9)	58 (22.1)	NS

SD: Standard deviation, n: number, MPV: Mean platelet volume, PCT: Platecrite, PDW: Platelet distrubution width, RDW: Reticulocytes distrubution width

Table 3. *Univariable and multivariable logical regression analysis of factors for ulcer diagnosed patients*

	Univariate				**Multivariate**			
	OR	Confidence Interval Lower	Upper	P value	OR	Confidence Interval Lower	Upper	P value
Age	1,014	1,001	1,026	0,028	1,016	1,002	1,031	0,030
Female	1,028	0,829	1,276	0,800	0,997	0,784	1,268	0,980
Hemoglobin	1,031	0,944	1,126	0,500	1,054	0,619	1,794	0,847
RDW_(1)	Baseline	—-	—-	0,775	—-	—-	—-	0,800
RDW_(2)	1,028	0,734	1,441	0,870	1,005	0,701	1,440	0,979
RDW_(3)	1,028	0,723	1,461	0,880	0,983	0,669	1,442	0,928
RDW_(4)	0,802	0,531	1,212	0,295	0,784	0,474	1,297	0,343
Hematocrites	1,010	0,980	1,041	0,521	0,982	0,821	1,176	0,846
PCT	0,575	0,050	6,630	0,658	1,406	0,043	45,966	0,848
MPV	1,012	0,899	1,138	0,847	0,988	0,833	1,172	0,893
PDW	0,969	0,908	1,034	0,340	0,971	0,895	1,053	0,478
PLT	0,999	0,996	1,001	0,361	0,998	0,994	1,002	0,291
Urea	1,001	0,996	1,005	0,677	1,000	0,994	1,005	0,875
Melena	1,048	0,845	1,300	0,670	1,022	0,790	1,323	0,866
Syncope	0,840	0,680	1,037	0,105	0,800	0,616	1,039	0,095
Druguse	1,326	0,942	1,866	0,105	1,140	0,773	1,680	0,509
CLD	3,181	1,082	9,354	0,036	3,431	1,145	10,280	0,028
HF	2,000	0,850	4,704	0,112	1,947	0,774	4,899	0,157

OR: Odds ratio, RDW: Reticulocytes distrubution width, PCT: Platecrite, MPV: Mean platelet volume, PDW: Platelet distrubution width, PLT: Platelets, CLD: Chronic liver disease, HF: Heart Failure

There were no differences in blood cell characteristics (RDW subgroups, PCT, MPV, PDW) or demographics between patients in Forrest I and Forrest II groups (Table 2).

Results of univariable and multivariable logistic regression analysis of factors associated with ulcer diagnosis are presented in Table 3. Only advanced age and presence of CLD were related to re-bleeding risk.

Table 4. *Statistically significant results in comparisons of baseline blood tests and patient demographics among the four RDW groups*

	RDW 1 (n:37)	RDW 2 (n:150)	RDW 3 (n:127)	RDW 4 (n:82)	P Value
Age, mean, SD	50.32 ± 22.77	63.27 ± 16.94	68.45 ± 17.36	69.28 ± 15.29	< 0.001
Hemoglobin, mean, SD	10.75 ± 2.18	9.66 ± 2.17	8.88 ± 2.41	8.46 ± 2.25	< 0.001
Hematocrite, mean, SD	32.12 ± 6.32	29.05 ± 6.52	26.95 ± 7.13	26.34 ± 6.53	< 0.001
MPV, mean, SD	10.56 ± 0.78	10.00 ± 1.39	9.17 ± 1.93	8.91 ± 2.05	< 0.001
PDW, mean, SD	12.29 ± 1.93	12.92 ± 2.90	14.31 ± 3.13	15.27 ± 3.56	< 0.001
PLT, mean, SD	216.38 ± 55.14	232.05 ± 66.70	243.18 ± 87.80	265.89 ± 105.04	0.006
Urea, mean, SD	65.81 ± 34.28	80.99 ± 39.95	92.58 ± 50.77	87.87 ± 49.89	0.009

RDW 1 group (RDW<12.8%); RDW 2 group (RDW 12.9–14.4%); RDW 3 group (RDW 14.5–16.5%); RDW 4 group (RDW > 16.6%);
RDW: Reticulocytes distrubution width, SD: Standard deviation, MPV: Mean platelet volüme, PDW: Platelet distrubution width, PLT: Platelets

Comparisons of baseline blood tests and patient demographic characteristics among the four RDW groups are presented in Table 4. Haemoglobin, haematocrit and MPV were lower in the high RDW groups (3 and 4) than the low RDW groups (1 and 2). Urea level, platelet count, PDW and mean age were higher in the high RDW groups (3 and 4) than the low RDW groups (1 and 2; $P < .05$).

DISCUSSION

AUGIB accounts for a significant portion of emergency department visits and is a cause of serious mortality and morbidity. In this study, duodenal ulcer, gastric ulcer, and oesophageal variceal bleeding were the most common causes of gastrointestinal bleeding. Early diagnosisof AUGIB and early risk stratification improve prognosis. Early identification and treatment of patients who require endoscopy is helpful. Many factors affect severity of gastrointestinal bleeding and re-bleeding risk (7-10).

Recent studies suggest possible biomarkers for determining gastrointestinal bleeding severity. In a study of paediatric patients with Henoch-Schönlein purpura, MPV levels were low among patients with UGIB (15). When acute blood loss occurs, MPV is expected to decrease, whereas platelets are expected to increase (16). However, MPV was higher among patients with UGIB compared with a control group of healthy volunteers in a study Tanoğlu et al.;the authors suggest that this change resulted from sympathetic activity related to hypovolemia and hypotension (17). Changes to platelet shape, size, and function may result from platelet activation in response to improved sympathetic activity (18, 19).

Variations in erythropoietin level and erythropoietin non-responsiveness are related to RDW levels. RDW can be seen physiologically in pregnant persons, black persons, and those who exercise heavily (20, 21). Various studies suggest that RDW is an independent risk factor for mortality and morbidity among persons with cancer, diabetes, cardiovascular disease, thromboembolic disease, kidney or liver disease, and inflammatory disease (22-25). RDW may also be related to risk associated with percutaneous coronary angiographic intervention and development of cancer following trauma. In major bleeding, venous inflammation and thrombosis mayincrease inflammatory cytokines, which in turn supress erythrocyte maturation. It has been suggested that suppression of erythrocyte maturation increases RDW (11, 13).

In this study,endoscopic Forrest classification was used to divide patients into two groups based on endoscopic findings related to gastric or duodenal ulcers. Demographic characteristics and laboratory parameters were compared between groups. In this preliminary exploration of biomarkers potentially associated with bleeding risk, RDW, PLT, PCT, MPV, and PDW levels did not differ by re-bleeding risk. Furthermore, there were no differences in re-bleeding risk by RDW subgroup. Haemoglobin, haematocrit, and MPV were lower in the high RDW groups (3 and 4) than the low RDW groups (1 and 2). However, urea, PLT, PDW, and mean age were higher in the high RDW groups (3 and 4) than the low RDW groups (1 and 2).

Our study should be considered in light of its retrospective design that used existing hospital records only.

In conclusion, AUGIB is among the most common reasons for seeking emergency medical services. Early diagnosis and treatment is important for a favourable prognosis. Although UGE is useful in diagnosing and treating these patients, rapid, practical, easy-to-use, and inexpensive biomarkers are needed to determine bleed-

ing severity. Our study showed that there were no differencesin these blood count parameters among patients with gastrointestinal ulcers who were at high risk and increased risk of re-bleeding. Future, prospective, randomized controlled studies should address this question.

Abbreviations

AUGIB — Acute upper gastrointestinal bleeding
RDW — Red blood cell distribution width
PCT — Plateletcrit
MPV — Mean platelet volume
PDW — Platelet distribution width

Acknowledgement:

None

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Licensing

Sažetak

KOEFICIJENT VARIJACIJE DISTRIBUCIJE ERITROCITA I TROMBOCITA KAO PREDIKTORA U UTVRĐIVANJU PROGNOZE KRVARENJA IZ GORNJIH PARTIJA GASTROINTESTINALNOG TRAKTA

Abaylı Bahri,[1] Gencdal Genco[2]

[1] Cukurova Dr. Askım Tufekci Hospital, Department of Gastroenterology and Hepatology, Adana, Turkey
[2] Istanbul Atasehir Memorial Hospital, Department of Gastroenterology, Istanbul, Turkey

Uvod i cilj: Akutno krvarenje iz gornjeg dela gastrointestinalnog trakta (AUGIB) je jedno od najčešćih urgentnih stanja u medicini. Rana detekcija pacijenata, koji su pod rizikom je od velikog benefita u pogledu lečenja i prognoze. Istraživali smo da li je težina ulkusne bolesti povezana sa koeficijentom varijacije distribucije eritrocita (RDW), zapreminskim udelom trombocita (PCT), srednjjom vrednošću trombocita (MPV) i koeficijentom distribucije trombocita (PDW).

Materijal i metode: Svi pacijenti, koji su se javili u urgentno odeljenje sa AUGIB u periodu od januara 2014. do juna 2014. godine bili su uključeni u studiju. Endoskopski nalazi, kompletna krvna slika, demografske karakteristike pacijenata, i endoskopski rezultati su bili sakupljani retrospektivno iz bolničke dokumentacije. Pacijenti sa stadijumom I ili stadijumom II ulkusa (određivanoj prema Forrest klasifikaciji) bili su upoređivani u pogledu ovih parametara. **Rezultati:** Ukupno 373 pacijenta i 211 pacijentkinja uzrasta 66,36 ± 17,36 godina su uključeni u studiju. Ulkus je bio dijagnostikovan kod 396 od 584 pacijenta (67,8%). Nije pronađena statistički značajna razlika u pogledu RDW-a ili trombocita između grupa.

Zaključak: Pacijenti koji boluju od AUGIB trebaju biti podvrgnuti urgentnoj dijagnostici i tretmanu. U ovoj studiji pacijenti sa AUGIB, grupisani prema etiologiji krvarenja, verovatni rani prognostički parametri nisu bili povezani sa težinom krvarenja u grupi pacijenata sa dijagnostikovanim gastričnim ili duodenalnim ulkusom.

Ključne reči: endoskopija, gastrointestinalno krvarenje, ulkus, RDW, PCT, MPV, PDW.

REFERENCES

1. Barkun A, Bardou M, Marshall JK; Nonvariceal upper GI bleeding consensus conference group. Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med. 2003; 139(10): 843-57.

2. Barkun AN, Bardou M, Kuipers EJ, Sung J, Hunt RH, Martel M, et al. International Consensus Upper Gastrointestinal Bleeding Conference Group. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med. 2010; 152(2): 101-13.

3. Hwang JH, Fisher DA, Ben-Menachem T, Chandrasekhara V, Chathadi K, Decker GA, et al. Standards of practice committee of the American Society for Gastrointestinal Endoscopy. The role of endoscopy in the management of acute non-variceal upper GI bleeding. Gastrointest Endosc. 2012; 75(6): 1132-8.

4. Gralnek IM, Dumonceau JM, Kuipers EJ, Lanas A, Sanders DS, Kurien M, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2015; 47(10): a1-46. Epub 2015 Sep 29.

5. Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med. 1994; 331(11): 717–27.

6. Holster IL, Kuipers EJ. Management of acute nonvariceal upper gastrointestinal bleeding: current policies and future perspectives.World J Gastroenterol. 2012; 18(11): 1202–7.

7. Nable JV, Graham AC. Gastrointestinal bleeding. Emerg Med Clin North Am. 2016; 34(2): 309–25.

8. Dabbah S, Hammerman H, Markiewicz W, Aronson D. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. Am J Cardiol. 2010; 105(3): 312–7.

9. Braun E, Domany E, Kenig Y, Mazor Y, Makhoul BF, Azzam ZS. Elevated red cell distribution width predicts poor outcome in young patients with community acquired pneumonia. Crit Care. 2011; 15(4): R194.

10. Hampole CV, Mehrotra AK, Thenappan T, Gomberg-Maitland M, Shah SJ. Usefulness of red cell distribution width as a prognostic marker in pulmonary hypertension. Am J Cardiol. 2009; 104(6): 868–72.

11. Fatemi O, Torguson R, Chen F, Ahmad S, Badr S, Satler LF, et al. Red cell distribution width as a bleeding predictor after percutaneous coronary intervention. Am Heart J. 2013; 166(1): 104–9.

12. Altintas O, Duruyen H, Baran G, Baran O, Katar S, Antar V, et al. The relationship of hematoma growth to red blood cell distribution width in patients with hypertensive intracerebral hemorrhage. Turk Neurosurg. 2017; 27(3): 368–73.

13. Paulus EM, Weinberg JA, Magnotti Lj, Sharpe JP, Schroeppel TJ, Fabian TC, et al. Admission red cell distribution width: a novel predictor of massive transfusion after injury. Am Surg. 2014; 80(7): 685–9.

14. Forrest JA, Finlayson ND, Shearman DJ. Endoscopy in gastrointestinal bleeding. Lancet. 1974; 2(7877): 394-7.

15. Makay B, Türkyılmaz Z, Duman M, Ünsal E. Mean platelet volume in Henoch-Schönlein purpura: relationship to gastrointestinal bleeding. Clin Rheumatol. 2009; 28(10): 1225-8.

16. Giles C. The platelet count and mean platelet volume. Br J Haematol. 1981; 48(1): 31–7.

17. Tanoglu A, Eroglu M, Osman Yildirim AO, Kara M, Yazgan Y. Increased Mean Platelet Volume Is Associated With Duration Of Hospitalization And Transfusion Requirement In Upper Gastrointestinal Bleedings. Gulhane Med J. 2015; 57(1): 16-20.

18. Thompson CB, Eaton KA, Princiotta SM, Rushin CA, Valeri CR. Size dependent platelet subpopulations: relationship of platelet volume to ultrastructure, enzymatic activity, and function. Br J Haematol. 1982; 50(3): 509–19.

19. Hjemdahl P, Larsson PT, Wallén NH. Effects of stress and beta-blockade on platelet function. Circulation. 1991; 84(suppl 6): VI44–61.

20. Kario K, Matsuo T, Nakao K, Yamaguchi N. The correlation between red cell distribution width and serum erythropoietin titres. Clin Lab Haematol. 1991; 13(2): 222–3.

21. Afsar B, Saglam M, Yuceturk C, Agca E. The relationship between red cell distribution width with erythropoietin resistance in iron replete hemodialysis patients. Eur J Intern Med. 2013; 24(3): e25–9.

22. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci. 2015; 52(2): 86–105.

23. Dabbah S, Hammerman H, Markiewicz W, Aronson D. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. Am J Cardiol. 2010; 105(3): 312–7.

24. Braun E, Domany E, Kenig Y, Mazor Y, Makhoul BF, Azzam ZS. Elevated red cell distribution width predicts poor outcome in young patients with community acquired pneumonia. Crit Care. 2011; 15(4): R194.

25. Patel KV, Ferrucci L, Ershler WB, Longo DL, Guralnik JM. Red blood cell distribution width and the risk of death in middle-aged and older adults. Arch Intern Med. 2009; 169(5): 515–23.

Correspondence to/Autor za korespondenciju
Genco Gençdal
Address: Istanbul Atasehir Memorial Hospital,
Department of Gastroenterology, GOP, Istanbul, Turkey
Phone Number: 090-0216-5706666 090-5063581760
E-mail: gencogencdal@yahoo.co.uk
Fax Number: 090-216-5706620

SANAMED
2019; 14(2): 175–180
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i2.315
UDK: 616.2(549)"2015/2016"
ID: 278334476
Original article

FREQUENCY OF DISEASES PRESENTING IN ENT OPD AT AYUB TEACHING HOSPITAL ABBOTTABAD

Qayyum Fahad Shah,[1] Fayyaz Salma[2]

[1] Ayub Medical College, Abbottabad, Pakistan
[2] Al-Muslim Public School Battagram, Mansehra, Pakistan

Primljen/Received 30. 01. 2019. god. Prihvaćen/Accepted 06. 06. 2019. god.

Abstract: **Introduction:** Patient presents with ear, nose and throat diseases in ENT OPD to otolaryngologist/ENT specialist. ENT diseases are serious public health problems because of their universal distribution the morbidities which they cause due to inherent physiological function that take place in head and neck region. Objectives of our study were to know frequency of ENT diseases in patients presenting at ENT OPD at Ayub Teaching Hospital Abbottabad.

Methods: A cross sectional study was done in Ayub Teaching Hospital Abbottabad from December 2015. to August 2016. Patients presenting at ENT OPD of Ayub Teaching Hospital Abbottabad were selected for study. Data about their ENT problems and concerned information were collected from them through well structured questionnaire. Data after collection was entered and analysed using SPSS-16.

Results: The minimum age is 1 and maximum age is 80 years. Out of total 250 patients, 129 (51.6%) were males and 121 (48.4%) were females, majority of patients 181 (72.4%) were from Abbottabad and majority of patients 165 (66.0%) were poor. The most common cases in ENT OPD were bilateral ear wax 15.2% followed by acute otitis media 13.2% and allergic rhinitis 13.2%.

Conclusion: It is concluded from our research that most common problems of ENT disorders are bilateral ear wax, allergic rhinitis, acute otitis media, chronic supporative otitis media and deviated nasal septum. The most common causes are infection, poor hygiene and poor nutrition.

Key words: Frequency, ENT diseases, Otitis media, ENT OPD patients of Ayub Teaching Hospital, Abbottabad.

INTRODUCTION

Patient presents with ear, nose and throat diseases in ENT OPDto otolaryngologist/ ENT specialist (1). The pattern of ENT diseases is quiet variable depending on age and group varying from community to community. They may be congenital or acquired in origin. Acquired diseases may be infectious, inflammatory, neurological and vascular or they may be due to some trauma. Complications occur in hearing, breathing, phonation, swallowing, speech, olfaction, taste and protection of lower respiratory tract (2).

In ENT OPD the most presenting ear diseases are ear infection, conductive hearing loss, otitis externa and chronic otitis media (3). The otitis media is the most common disease in young patient because of its more horizontal orientation in children than adults (4). In a survey done by WHO chronic suppurative otitis media (CSOM) was reported to be the most common cause of hearing loss in children in developing countries. Survey on prevalence of CSOM have shown the global burden of illness from CSOM involves 65-330 million individuals 60% of whom suffer from significant defect (5). In ear diseases oral medication response is excellent while surgical intervention is less frequently required (6).

Diseases of nose which presents the ENT OPD are nasal deformities, tumours, disease of nasal vestibule, nasal septum deviation, nasal polyps, rhinitis, epistaxis, etc. Causes of nasal diseases are trauma, nose surgery and infections. Complication that occurs due to nasal diseases are meningitis, cavernous sinus thrombosis and septal abscess (7). Acommon problem of nose affecting 60 million Africans each year is epistaxis. Most of its cases are minor and manageable but some presents as a life threatening problem. Common local causes are trauma, anatomical deformities and tumours. Cardiovascular diseases and hypertension are its systemic causes (8). Epistaxis is a common problem in children in Kiesselbach area due to local irritation in children (9). Epistaxis is initially treated by first aid measures but other times need some special measures to treat (10).

Most common throat diseases in outdoor patient department are sore throat, tonsillitis, pharyngitis and cancers. Causes of throat disease are usually a viral infection but other causes include allergies. Complication of throat diseases is acute rheumatic fever; acute glomerular nephritis and peritonsillar abscess formation (11). Second most common cancer of the respiratory tract is the laryngeal cancer. Risk factor for this type of cancer is cigarette smoking, alcohol consumption and may be human papilloma virus 16 and helicobacter pylori (12). Incidence of multiple primary tumours in head and neck region ranges from 10-35 percent (13).

In head and neck malignancies laryngeal cancer accounts approximately for 20% of all cases. Treatment for laryngeal include total laryngectomy (Tl), alone or with neck dissection (ND), radiotherapy alone (RT), TL followed by RT and combined chemotherapy (14).

Children going to schools are more prone to ENT diseases because of cross infections. This chronic problem not only hampers developmental progress and school performance but also cause physical and emotional suffering (15). Foreign bodies in ear usually found in children below age of ten years it may be iatrogenic or accidental. Tracheobronchial foreign bodies are the major cause of mortality and morbidity in paediatric age group (16).

It has been concluded from a study carried out in India that smoking is the main cause of middle ear diseases in children and adults .Among adults hearing loss is more common with smoking (17).

According to a study done in Peshawar the incidence of common ENT diseases presenting in OPD are chronic tonsillitis 37%, CSOM 14%, rhinitis due to deviated nasal septum 67%.

A study done on prevalence of allergic rhinitis in Oman showed that 7% patients with nasal symptoms attended the ENT OPD (18). A study performed in France on allergic rhinitis and itžs affect on sleep showed that sleep impairment was significantly worse with allergic rhinitis. Everyday living is also impacted by allergic rhinitis due to lack of sleep (19). Studies showed that aeroallergens are the primary triggers for respiratory tract diseases (20).

Asthma is a worldwide common disease in children and adults (21). According to a report of WHO asthma a life threatening disease roughly effect 100 and 150 million people around the globe and over 180,000 deaths occur from this condition annually. About 8% of Swiss population suffers from asthma. There are about 3 million asthmatics in Japan and 4 million in Germany. A rough estimate in India indicates a prevalence of between 10% and 15% in 5-11 year old children (22). The prevalence of asthma in Pakistan is increasing day by day with an annual increase of 5% of which 20% to 30% are children between 13 and 15 years of age. Nearly 20 million people about 12% of Pakistani adult population are suffering from disease (23).

According to a study done at Military Hospital Attockotomycosis (a fungal ear infection common in tropical countries) is a common condition often seen in ENT OPD and in this study its prevalence is about 7% among patients who presented with sign and symptoms of otitis media. Its various predisposing factors are humid climate, presence cerumen, instrumentation of ear and increase use of antibiotics (24). Otitis media with effusion is also a common medical in Indian children and its prevalence has been quoted 16.6% in children of age 5 to 7 (25). According to a report of WHO 5% of world population 360 million people has disabling hearing loss (a person who is not able to hear as well as someone with normal hearing _hearing threshold of 20 decibel or below in both ears is to have hearing loss) (26).

A study done on symptoms of ENT diseases showed that headache was the main symptom in patients presented in ENT OPD (27).

A study done on ear ,nose and throat diseases showed that common ear, nose and throat disorders were seen in patients aged < 15 years are otitis media, obstructive adenoids and foreign bodies in the ear whereas hearing loss, rhino sinusitis and tumours were the common disorder of ENT in patient aged 16 years and above (28).

Chronic rhino sinusitis (CRS) a clinical syndrome characterized by mucosal infection of nose and paranasal sinuses is one of the most prevalent chronic diseases worldwide. It is the second most chronic condition in United States, affecting one in seven American adults (29). In USA prevalence of sinusitis is estimated to be 14% of global population. Patients with particular disease more often develop sinusitis such as 25-30% of allergic patients, 43% of asthmatic patients, 37% of patients with transplants and 54-68% of patients with AIDS (30). Studies from tertiary care centres indicate a high prevalence of fungal rhino sinusitis in India. This was found in 70% young males in 10-39 years age group from rural India (31).

MATERIAL AND METHODS

This was a cross sectional descriptive type of study at Ayub Teaching Hospital Abbottabad. The study was done over a period from December 2015 to June 2016. The sample size was 250. Non Probability convenient sampling. Patients with different ENT diseases presenting at ENT OPD of Ayub Teaching hospital Abbottabad were included. All patients who are in emergency condition were excluded. Data was collected using a structural questionnaire after pretesting. The data after collection was entered and analyzed using statistical software SPSS-16. Mean and standard deviation were calculated

for quantitative variables like age, monthly family incomes etc. while frequencies and percentages were calculated for categorical variables like gender, socioeconomic etc. Results were displayed as tables and graphs.

RESULTS

Table 1. *Gender of patients*

	Frequency	Percentage (%)
Male	129	51.6%
Female	121	48.4%
Total	250	100%

Table 1 shows that out of total 250 patients, 129 (51.6%) were males and 121 (48.4%) were females.

Table 2. Socioeconomic status

	Frequency	Percent
Poor	165	66.0%
Middle	72	28.8%
Upper	13	5.2%
Total	250	100.0%

Table 2 shows that majority 165(66%) of patients were poor, 72 (28.8%) belonged to middle class and 13 (5.2%) were from upper class.

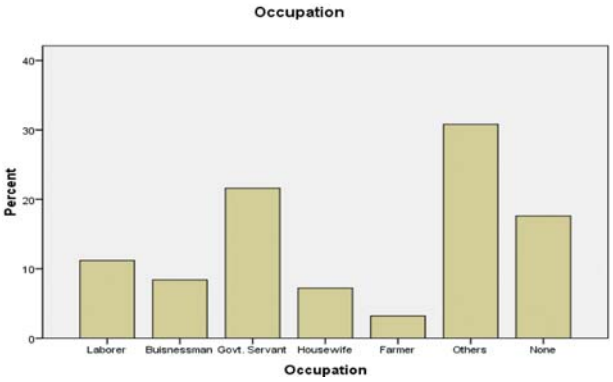


Figure 1. *Occupation*

Figure 1 shows that out of 250 patients, 28 (11.2%) were laborer, 21 (8.4%) were businessman, 54 (21.6%) were government servant, 18 (7.2%) were housewife, 8 (3.2%) were farmers, 77 (30.8%) had other jobs and 44 (17.6%) had no jobs.

Table 3 shows that out of total 250 patients, 33 (13.2%) were suffering from acute otitis media, 21 (8.4%) had acute pharyngitis, 11 (4.4%) had acute sinusitis, 13 (5.2%) had acute tonsillitis, 33 (13.2%) had allergic rhinitis, 38 (15.2%) had bilateral ear wax, 10 (4.0%) had chronic pharyngitis, 27 (10.8%) had chronic supporative otitis media, 26 (10.4%) had chronic tonsillitis, 20 (8.0%) had deviated nasal septum, 7 (2.8%) had epistaxis and 11 (4.4%) were suffering from otitis externa.

Table 3. *Diagnosis*

	Frequency	Percent
Acute otitis media	33	13.2%
Acute pharyngitis	21	8.4%
Acute sinusitis	11	4.4%
Acute tonsillitis	13	5.2%
Allergic rhinitis	33	13.2%
Bilateral ear wax	38	15.2%
Chronic pharyngitis	10	4.0%
Chronic supporative otitis media	27	10.8%
Chronic tonsillitis	26	10.4%
Deviated nasal septum	20	8.0%
Epistaxis	7	2.8%
Otitis externa	11	4.4%
Total	250	100.0%

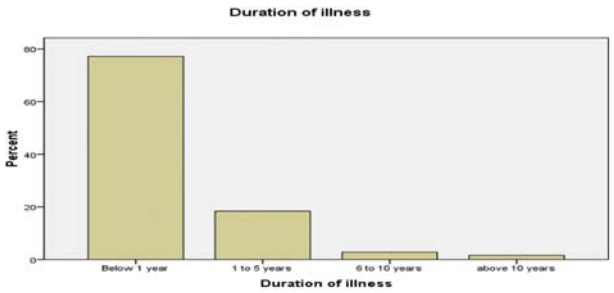


Figure 2. *Duration of illness*

Figure 2 shows that out of total 250 patients, 193 (77.2%) patients had duration of illness below 1 year, 46 (18.4%) had 1 to 5 years, 7 (2.8%) had 6 to 10 years and 4 (1.6%) had above 10 years duration of illness.

Table 4. *Nature of visit*

Nature of visit	Frequency	Percent
First	117	46.8
Follow up	133	53.2
Total	250	100.0

Table 4 shows that out of total 250 patients, 117 (46.8%) patients had first visit to hospital and 133 (53.2%) patients were follow up.

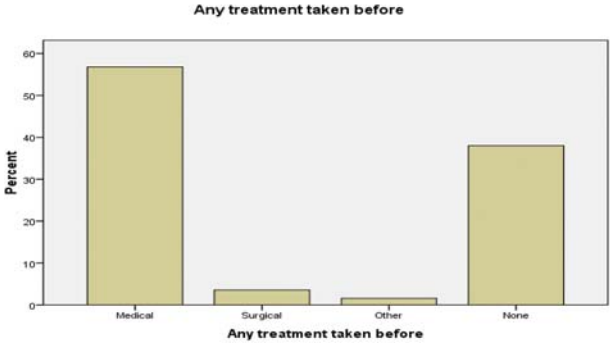


Figure 3. *Any treatment taken before*

Figure 3 shows that out of total 250 patients, 142 (56.8%) had taken medical treatment, 9 (3.6%) had taken surgical treatment, 4 (1.6%) had taken other treatment and 95 (38.0%) had taken no treatment before.

DISCUSSION

The pattern of ENT disease is quiet variable depending on age & group varying from community to community. A prospective cross sectional study of all consecutive patients coming to otolaryngology clinic in Oman was done on allergic Rhinitis and associated co morbidities. In this study allergic Rhinitis was noted in 48% of patients. According to our study out of 250 cases 33 patients (13.2%) were of allergic rhinitis. The difference in result is due to sample size which is small in our study (18).

A study done in India on the Prevalence of preventable ear disorders in primary school children (aged 5 to 12 years) through pro-forma questionnaire in 15718 primary school children. Most common ENT disorders seen in these children were Ear wax in 7.93%, chronic otitis media in 4.79% & 3.66% suffered from otitis media with effusion. Acute otitis media was detected in 0.65% children and foreign bodies were found in 0.34%. According to our study, out of 250 patients of bilateral ear wax are (15.2% , chronic otitis media 10.8% and acute otitis media 13.2%. Difference in results is due to sample size and age groups (32).

In our study patient occupational classes showed that there were more patients in lower occupational classes than in those in upper classes. Same results are showed by a study done in England by SL Isaac et al (33). A prospective study carried out at ENT department of KMC Peshawar Pakistan from April 2011 to May 2012 a total of 32800 patients showed the distribution of diseases systemically that is ear diseases were 47%, 36% Nasal complaints and 17% Laryngopharyngeal. In our study ear diseases are 43.6%. Nasal complaints are 28% and 28.4% complaints are of Laryngopharyngeal problems. The difference in frequency distribution is due to large size (4).

A prospective study was conducted at tertiary care hospital in Peshawar Pakistan. Most of the ENT disorders were diagnosed in those infants were Pharyngitis (30%) Otitis media 29.33%, tonsillitis (25.33%) and Nasal Obstruction (5.3 %.) This study shows that ENT, diseases are more common in children (34). In our study cases of tonsillitis are 16%, Pharyngitis 12.4% and otitis media 24%. Results are different because of difference in age group.

A study done in Nepal on prevalence of ENT diseases in children shows that low socioeconomic status, overcrowding & joint families might be responsible for the high prevalence of ENT diseases (35).

CONCLUSION

From this study, frequency of ENT diseases among patients presenting at ENT OPD at Ayub Teaching Hospital Abbottabad, we concluded that 15.2% patients had bilateral ear wax, 13.2% had allergic rhinitis and acute otitis media, 10.8% had chronic suppurative otitis media, 10.4% had chronic tonsillitis, 8.4% had acute pharyngitis, 8% had deviated nasal septum, 5.2% had acute tonsillitis, 4.4% had acute sinusitis and otitis externa, 4% chronic pharyngitis and 2.8% had epistaxis. The main determinant is that ENT diseases are more in males and lower socio-economic families because of poor nutrition, poor housing and poor hygiene.

This study shows that allergic rhinitis, bilateral ear wax acute and chronic suppurative otitis media and pharyngitis are the common ear, nose and throat disorders.

Abbreviations

ENT — Ear, Nose and Throat (Otorhinolaryngology)
OPD — Outpatient department
SPSS — Statistical Package for the Social Sciences
WHO — World health organization
CSOM — chronic supprative otitis media
TL — Total laryngectomy
ND — Neck dissection
RA — Radiotherapy alone
CRS — Chronic rhino sinusitis
USA — United States of America
AIDS — Acquired immunodeficiency syndrome

Conflict of Interest

No author has any potential conflict of interest.

Financial Disclosure

The work received no external financial support.

Sažetak

UČESTALOST OBOLJENJA KOD PACIJENATA PREGLEDANIH U ORL AMBULANTI U AJUB UNIVERZITETSKOJ BOLNICI ABBOTTABAD

Qayyum Fahad Shah,[1] Fayyaz Salma[2]

[1] Ayub Medical College, Abbottabad, Pakistan
[2] Al-Muslim Public School Battagram, Mansehra, Pakistan

Uvod: Pacijent se ambulantno javlja specijalisti otorinolaringologije zbog poremećaja uva, grla i nosa. Oboljenja koja zahvatuju regiju uha, grla i nosa su ozbiljni javno zdravstveni problem prvenstveno zbog njihove univerzalne distribucije morbiditeta, koja zahvata region glave i vrata. Ciljevi naše studije bili su da se uoči frekventnost ORL bolesti kod pacijeata, koji se javljaju specijalisti otorinolaringologije u Ajub Univerzitetskoj Bolnici Abotabad.

Metod: Ova studija izvedena je u Ajub Univerzitetskoj Bolnici Abotabad u periodu od decembra 2015. do avgusta 2016. godine. Pacijenti koji su se javili specijalisti otorinolaringologije u Ajub Univerzitetskoj bolnici Abotabad bili su uključeni u studiju. Podaci vezani za ORL simptomatologiju, kao i ostale informacije od značaja, bili su sakupljani kroz dobro strukturisan upitnik. Podaci nakon sakupljanja su kompjuterski uneti i obrađivani koristeći SPSS-16.

Rezultati: Najmlađi pacijent je imao 1 godinu, a najstariji 80 godina. Od ukupno 250 pacijenata, 129 (51,6%) su bili muškarci, a 121 (48,4%) žene. Štaviše većinu pacijenata, 181 (72,4%) činili su stanovnici Abotabada i većina njih je bila niskog materijalnog stanja i to 165 (66,5%). Najčešći broj pacijenata je imao obostrano zapušenje spoljašnjeg ušnog kanala, zbog povećane ušne masti (15,2%), na drugom mestu su pacijenti sa akutnim zapaljenjem srednjeg uha (13,2%) i oni sa alergijskim rinitisom, koji je imalo 13,2% ispitanika.

Zaključak: Može se zaključiti iz naše studije da je najčešći problem ORL patologije obostrano zapušenje spoljašnjeg ušnog kanala ušnom masti, alergijski rinitis, akutni otitits media, hronični supurativni otitis media i devijacija nosne pregrade. Najčešći uzrok su infekcije, slaba higijena i smanjena uhranjenost.

Ključne reči: učestalost, ORL bolesti, otitis media.

REFERENCES

1. MedicineNet. Definition of ENT [online].[cited on 2016 Jan 25] Available from URL: http://www.medicinenet.com/script/main/art.asp?articlekey=3252

2. Fasunla AJ, Samdi M, Nwaorgu OG. An audit of Ear, Nose and Throat diseases in a tertiary health institution in South-western Nigeria. Pan Afr Med J. 2013; 14(1) 6-12.

3. Seth Scott Bishop Diseases of the Ear, Nose, and Throat and Their Accessory Cavities: A Condensed Text-Book. FA Davis Company, 1897.

4. Khan AR, Khan SA, Arif AU, Waheed R. Analysis of ENT diseases at Khyber teaching hospital, Peshawar. J Med Sci. 2013; 21(1): 7-9.

5. World health organization. Chronic suppurative otitis media [online]. [cited on 2016 Feb 10] Available from URL: http: //www. who.int/pbd /publications/ Chronic suppurative otitis_media.pdf.

6. Finnbogadottir AF, Petersen H, Laxdal T, Gudbrandsson F, Gudnason T, Haraldsson A Mastoiditis in children in Iceland Laeknabladid. 2007; 93 (4): 275-80.

7. PL Dhingra, Shruti Dhingra, Textbook of diseases of Ear, Nose and Throat and Head and Neck surgery. 6th ed. Elsevier publisher; 2014.

8. Fatakia A, Winters R, Amedee RG. Epistaxis: a common problem. Ochsner J. 2010; 10(3): 176-8.

9. Guarisco JL, Graham 3rd HD. Epistaxis in children: causes, diagnosis, and treatment. Ear, nose, throat J. 1989; 68(7): 522-8.

10. Kucik CJ, Clenney T. Management of epistaxis. Am Fam Physician. 2005; 71(2): 305-11.

11. Mackenzie M. A manual of diseases of the throat and nose, including the pharynx, larynx, trachea, oesophagus, nose and, and nasopharynx. 1st ed. Willian wood and comp, New York. 1880.

12. Gong H, Shi Y, Zhou X, Wu C, Cao P, Xu C et al. Microbiota in the throat and risk factors for laryngeal carcinoma. Appl Environ Microbiol. 2014; 80(23): 7356-63.

13. Heroiu Cataloiu AD, Danciu CE, Popescu CR. Multiple cancers of the head and neck. MFdica. 2013; 8(1): 80-5.

14. Shaikh KR. Topographic distribution of laryngeal cancer. J Liaquat Uni Med Health Sci. 2007; 6(3): 124-6.

15. Hamid A, Sattar F, Din S. Prevalence rate and morbidity pattern of common ENT diseases and disorders in infants and children. Journal of Postgraduate Medical Institute (Peshawar-Pakistan). 1991; 5(2): 59-67.

16. Saha S, Chandra S, Mondal PK, Das S, Mishra S, Rashid MA et al. Emergency otorhinolaryngolocal cases in Medical College, Kolkata — a statistical analysis. Indian J Otolaryngol Head Neck Surg. 2005; 57(3): 219-25.

17. Gaur K, Kasliwal N, Gupta R. Association of smoking or tobacco use with ear diseases among men: a retrospective study. Tob Induc Dis. 2012; 10(1):4.

18. Al-Abri R, Bharghava D, Kurien M, Chaly V, Al-Badaai Y, Bharghava K. Allergic rhinitis and associated comorbidities: prevalence in oman with knowledge gaps in literature. Oman Med J. 2014; 29(6): 414-8.

19. Pillai A. Patients with severe allergic rhinitis are more often affected by sleep disorders. Thorax. 2007; 62(2): 130.

20. Ahmad F, Yousaf F, Asif S. Prevalence of allergic disease and related allergens in Pakistan in 2007. Journal of Postgraduate Medical Institute (Peshawar-Pakistan). 2011 21; 25(1): 14-23.

21. Adobamen PR, Egbagbe EE. Prevalence of Throat Symptoms in Asthmatic Patients in Nigeria. Pakistan Journal of Otolaryngology. 2013; 29:47-8.

22. World Health Organization. Bronchial Asthma. [online]. [cited on 2016 March 14]. Available from URL: http://www.who.int/mediacentre/factsheets/fs206/en/.

23. Chiesi Pakistan.Respiratory diseases [Šonline]. [cited on 2016 April 12]. Available from URL: http://www.chiesipakistan.com/index.php?page=Respiratory+Diseases.

24. Anwar K, Gohar MS. Otomycosis; clinical features, predisposing factors and treatment implications. Pak J Med Sci. 2014; 30(3): 564-7.

25 Sanli A, Tasdemir O, Eken M, Celebi O, Yilmaz SH. Prevalence of otitis media with effusion among primary school age-children and etiopathogenic examination. Indian Journal of Otolaryngology and Head & Neck Surgery. 2014; 66(1): 95-8.

26. World health organization. Prevalence of hearing loss [online]. [cited on 2016 April 13]. Avalible from URL: http://www.who.int/pbd/deafness/WHO_GE_HL.pdf.

27. Reck R. Headaches caused by ENT diseases. Radiologe. 1984; 24(8): 376-80.

28. Fasunla AJ, Samdi M, Nwaorgu OG. An audit of Ear, Nose and Throat diseases in a tertiary health institution in South-western Nigeria. Pan Afr Med J. 2013; 14:1.

29. Chaaban MR, Walsh EM, Woodworth BA. Epidemiology and differential diagnosis of nasal polyps.Am J Rhinol Allergy. 2013; 27(6): 473-8.

30. Van Cauwenberge P, Watelet J. Epidemiology of chronic rhinosinusitis. Thorax. 2000; 55(Suppl 2): S20-1.

31. Chakrabarti A, Rudramurthy SM, Panda N, Das A, Singh A. Epidemiology of chronic fungal rhinosinusitis in rural India. Mycoses. 2015; 58(5): 294-302.

32. Chadha SK, Sayal A, Malhotra V, Agarwal AK. Prevalence of preventable ear disorders in over 15000 schoolchildren in northern India. The Journal of Laryngology & Otology. 2013; 127(01): 28-32.

33. Isaacs SL, Schroeder SA. Class — the ignored determinant of the nation's health. N Eng J Med. 2004 ;351(11): 1137-42.

34. Hamid A, Sattar F. Prevalence rate and morbidity pattern of common ENT diseases and disorders in infants and children. Journal of Postgraduate Medical Institute (Peshawar-Pakistan). 2011; 5(2): 59-67.

35. Nepali R, Sigdel B. Prevalence of ent diseases in children: Hospital based study. The internet journal of otorhinolaryngology. 2012; 14(2): 1-5.

Correspondence to/Autor za korespondenciju
Dr. Shah Fahad Qayyum
Gohar Sons, Peeple Chowk
Nowshera cantt.
Pakistan
tel: 00923439149039
email: sfask2013@gmail.com

SANAMED
2019; 14(2): 181–184
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i2.306
UDK: 616.37-003.4
ID: 278324236
Case report

CHOLEDOCHOCELE WITH RECURRENT PANCREATITIS - CASE REPORT

Ates Fatih,[1] Kara Turgay,[1] Sara Halil İbrahim,[1] Coban Muhammed Sami,[1] Durmaz Mehmet Sedat,[2] Dal Fatih[3]

[1] Department of Radiology, University of Health Science, Konya Trainning and Research Hospital, Konya, Turkey
[2] Department of Radiology, Selcuk University Faculty of Medicine, Konya, Turkey
[3] Department of Surgery, Kayseri State Hospital, Turkey

Primljen/Received 16. 01. 2019. god.

Prihvaćen/Accepted 16. 04. 2019. god.

Abstract: Choledochal cysts are an uncommon anomaly of unknown etiology of the bilious system. This anomaly, characterized by cystic dilatations on intrahepatic or extrahepatic bile ducts, can be seen at any age from birth. Most rare congenital bile duct cysts choledochocele (type III) is usually diagnosed in adults. Since the congenital choledochal cyst has not a unique clinical finding, the basic criteria for diagnosis are based on imaging findings. This article presents a case of choledochocele accompanying recurrent pancreatitis in a 19-year-old male patient.

Key words: magnetic resonance cholangiopancreaticography, choledochocele, bilier duct.

INTRODUCTION

Congenital cystic lesions of the biliary tract affect the intrahepatic and extrahepatic bile ducts. Choledochal cysts are rare abnormalities manifested by cystic dilatation of the extrahepatic and/or intrahepatic biliary tree.

The clinical presentation of choledochal cysts occur before 10 years age in 80% of patients, usually the result of complications are cholangitis and pancreatitis (1).

Most rare congenital bile duct cyst, choledochocele (type III) is usually diagnosed in adults. Since the congenital choledochal cysts have not unique clinical finding, the basic criteria for diagnosis are based on imaging findings.

The first imaging modality in patients with suspected biliary system pathology is ultrasonography (US). It is an easily accessible noninvasive method. Sensitivity varies according to the practitioner, the presence of intraabdominal gas and the localization of the disease.

Magnetic Resonance cholangiopancreotography (MRCP) is a non-invasive method which can be preferred in the diagnosis of biliary tract pathologies with its features such as no ionizing radiation, no risk of complications, no need for patient preparation, feasibility during pancreatitis and cholangitis attack, and the ability to obtain images in different plans.

CASE REPORT

A 19-year-old male patient presented to the clinic with complaints of recurrent abdominal pain. The patient was diagnosed with choledochal cyst in 1999 and was followed up because of recurrent pancreatitis episodes in gastroenterology clinic. In laboratory analysis: WBC 8800 IU/L, HB: 14,5 U/L, platellets: 206000, glucose: 107 mg/dl, total bilirubin: 1,3, Direct bilirubin: 0,29, AST: 58 U/L, ALT: 19 U/L, LDH: 767 U/L, CK-MB: 84 U/L, Amylase: 146 U/L, Lipase: 157 U/L, CRP: 28.4 mg/L .Computed tomography (CT) of the

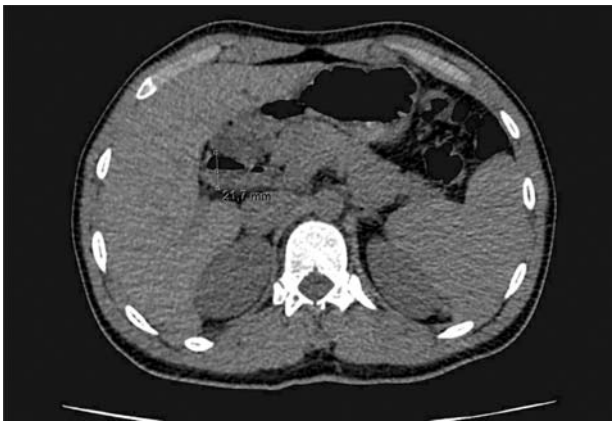


Figure 1*. In non contrast enhanced CT: common bile duct is dilated, measuring 22 mmin diameter*

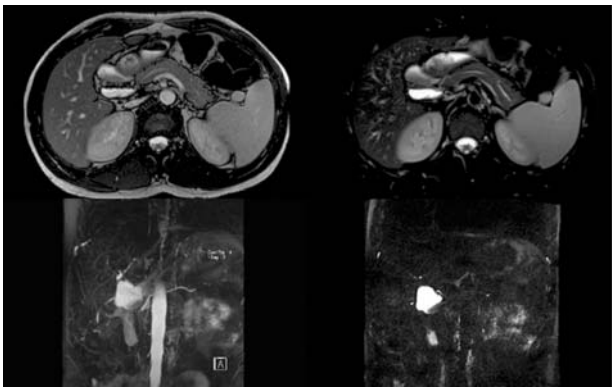


Figure 2. *In MRCP, the right intrahepatic main bile duct was normal width, the left main bile duct and intrahepatic bile ducts are evident, the diameter of the choledochus was increased in the middle segment andmeasured in the widest area as 33 x 15 mm compatible with choledochocele*

abdomen revealed that the common bile duct was dilated (22 mm in diameter) (Figure 1). Further MRCP was performed to the patient. In MRCP, the right intrahepatic main bile duct was in normal dimension, the left main bile duct and intrahepatic bile ducts were evident, the diameter of the choledochus was increased in the middle segment and measured in the widest area as 33 x 15 mm compatible with choledochocele (Figure 2). The gall bladder was operated and not observed. He had no hystory of choledochocele surgical treatment.

DISCUSSION

Biliary tract variations are very common. Knowing these variations reduces the risk of bile duct injury caused by laparoscopic cholecystectomy, percutaneous or endoscopic interventions.Aberrant right hepatic duct connected to the common hepatic duct or to the cystic duct, long cystic duct parallel to the common hepatic duct, cystic duct connected medially to the common hepatic duct, short cystic ductand a cystic duct connected to the distal third of the common hepatic duct are the anatomical variations associated with increased bile duct injury (2, 3, 4, 5).

In patients suffering with recurrent pancreatitis, cholangitis, choledocholithiasis or intermittent abdominal pain, jaundice and nausea; congenital anomalies of biliary tract should be considered in the differential diagnosis (5, 6).

Congenital biliary cystic disease is the cystic or fusiform dilatation of intra or extrahepatic biliary tract including choledochal cyst, choledochocele, choledochal diverticulum and Caroli disease. 80% of the lesions are observed in infancy and childhood. The classic triad of symptoms are right upper quadrant pain, abdominal mass and jaundice and are present in one third of patients. The most common complications of cysts are choledocholithiasis, cholelithiasis, cancer development, pancreatitis, cholangitis and cyst rupture. In our patient, there was recurrent pancreatitis. Excision of cysts eliminates cancer risk, but the possibility of developing cancer from intrahepatic bile ducts requires long-term follow-up (3, 7).

Todani classification system divides cystic lesions into 5 main categories. Type IA is cystic dilatation of the main bile duct, Type IB is the focal segmental dilatation, usually distal to the main bile duct and Type IC is the fusiform dilatation of the main bile duct and the main hepatic channel. Type II is the real diverticul of the extrahepatic channel. Type III is the choledococele. Type IVA is dilatation of intra and extrahepatic ducts (segmental cysts) and Type 4B is the dilatation of multiple segments of extrahepatic channels only. Type V is the Caroli disease (3).

CT, which is the second most frequent after US, is one of tht major diagnostic methods used in the diagnosis of hepatobiliary diseases and is becoming more important with the introduction of multislice devices. CT is performed in cases where US findings are not certain, when the mass is suspectable, distal of the common bile duct cannot be seen due to gas, and segmental obstruction is present (8). It is possible to perform mass characterization because it allows visualization in different phases (arterial, portal, venous) after intravenous contrast medium (9). CT is the first method in the diagnosis of gallbladder tumors. CT has an important role in diagnosing diseases and monitoring the complications that may cause serious complications such as cholecystitis and pancreatitis as well as space occupying lesions.The two most important disadvantages of CT are ionizing radiation exposure and hypersensitivity reactions that may develop with iodinated contrast agents (10).

MRCP was first emerged as a noninvasive method in the imaging of biliary tract in 1991 and it allows direct imaging of the biliary system without requiring contrast.The principle of MRCP is based on the increase in contrast between stationary or slow moving fluids (bile) and background soft tissues (liver, pancreas, abdominal fat) using heavy T2 A weighted sequences (11). In T2A weighted images, stationary fluids exhibit higher signal intensity, whereas the soft tissues in the background have low signal intensity (11, 12).

Radiological imaging methods have great importance in the evaluation of biliary tract. US is the first choice method because it is easily applicable and accessible in diseases of the pancreatic and biliary system. However, there are some limitations. The sensitivity depends on the operator. US can show the presence of dilatation in biliary tract but it may be insufficient

to reveal its cause.Therefore, additional examinations are needed (13, 14).

In these examinations, it was determined that effectivity of MRCP was close to ERCP examination which is accepted as the gold standard for visualization of biliary tract. The fact that ERCP is an invasive method, has a mortality rate of 0.2-1%, a morbidity risk of 1-7%, the need for experienced operators limits its use for diagnostic purposes.MRCP is a reliable and noninvasive method in the treatment of pancreatic and biliary system diseases. It does not require contrast media, allows multiplanar and cross-sectional imaging.Therefore, MRCP is a preferred method especially in complicated cases (13, 15, 16).

CONCLUSION

Intraoperative cholangiography and endoscopic retrograde cholangiopancreatography (ERCP) are important diagnostic methods for bile duct patholgies. However, due to the fact that clinical findings are not unique, choledococele suspicion rarely arises and ultrasonography (US) may be inadequate for diagnosis. ERCP is accepted as the gold standart method in diagnosis. However, since it is invasive, MRCP is preferred instead asnon-invasive, non-ionizing and easily applicable method. In such a group of patients in whom pancreatitis may occur as a complication, it was thought that the first-line MRCP could be used instead of ERCP, which would further increase the risk of complications, and that it could show a similar diagnostic success.

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

Sažetak

HOLEDOHOCELA SA REKURENTNIM PANKREATITISOM - PRIKAZ SLUČAJA

Ates Fatih,[1] Kara Turgay,[1] Sara Halil İbrahim,[1] Coban Muhammed Sami,[1] Durmaz Mehmet Sedat,[2] Dal Fatih[3]

[1] Department of Radiology, University of Health Science, Konya Trainning and Research Hospital, Konya, Turkey
[2] Department of Radiology, Selcuk University Faculty of Medicine, Konya, Turkey
[3] Department of Surgery, Kayseri State Hospital, Turkey

Ciste holedoha su neobične anomalije nepoznate etiologije bilijarnog sistema. Ova anomalija, koju karakteriše cistična dilatacija intrahepatičkih ili ekstrahepatičnih žučnih puteva, se može naći u bilo kojoj životnoj dobi. Najređa kongenitalna cista žučnih vodova, holedohocela (tip III) se obićno dijagnostikuje kod odraslih. S obzirom da kongenitalna cista holedohusa nema jedinstvenu kliničku manifestaciju, osnovni kriterijum za dijagnozu se zasniva na dijagnostičkim procedurama. Ovaj rad prezentuje prikaz slučaja holedohocele udružene sa rekurentnim pankreatitisom kod 19-godišnjem muškarca.

Ključne reči: magnetna rezonanca holangiopankreatografija, holedohocela, žučni kanal.

REFERENCES

1. Singham J, Yoshida EM, Scudamore CH. Choledochal cysts. Part 2. Diagnosis. Can J Surg 2009; 52(6): 506–11.

2. Mortele JK, Ros PR. Anatomic variants of the biliary tree: MR cholangiographic findings and clinical applications. AJR 2001; 177(2): 389-94.

3. Selçuk D, Aykut B. Safra kanalları, safra kesesi ve pankreasın MR görüntülenmesi In: Olgun DÇ.Tüm Vücut MRG Istanbul: Istanbul medikal yayıncılık. 2008; 63-147.

4. Halefoglu AM. Magnetic resonance cholangiopancreatography: A useful tool in the evaluation of pancreatic and biliary disorders. World J Gastroenterol 2007; 13(18): 2529-34.

5. Taourel P, Bret PM, Reinhold C, Barkun AN, Atri M. Anatomic variants of the biliary tree:Diagnosis with MR cholangiopancreatography. Radiology 1996; 199(2): 521-7.

6. Dohke M, Watanabe Y, Okumura A, Amoh Y, Oda K, Ishimori T, et al. Anomalies and anatomic variants of the biliary tree revealed by MR cholangiopancreatography. AJR 1999; 173(5): 1251-4.

7. Kim SH, Lim JH, Yoon HK, Han BK, Lee SK, Kim YI. Choledochal cyst: comparison of MR and conventional cholangiography. Clin Radiol. 2000; 55(5): 378-83.

8. Tuncel E. Klinik Radyoloji. 2.bask. Bursa: Nobel & Günes Kitabevi 2008: 498-513.

9. Cieszanowski A, Chomicka D, Andrzejewska M, PruszyAski B, Pawlak J, Mustafa AM, Imaging techniques in patients with biliary obstruction. Med Sci Monit. 2000; 6(6): 1197-202.

10. Tessler FN, Lockhart ME. The Biliary Tract. In: Lee JKT, Sagel SS, Stanley RS, Heiken JP (eds). Computed Body

Tomography with MRI Correlation. 4th ed. Volume 2. Philadelphia: Lippincott Williams & Wilkins. 2006; 931-8.

11. Ergen FB. Manyetik rezonans kolanjiyopankreatografi: klinik uygulamaları. Hacettepe Tæp Dergisi. 2006; 37: 72-7.

12. Pavone P, Laghi A, Panebianco V, Catalano C, Lobina L, Passariello R.MR cholangiography: techniques and clinical applications. Eur Radiol. 1998; 8(6): 901-10.

13. Bearcroft PW, Lomas DJ. Magnetic resonance cholangiopancreatography. Gut. 1997; 41: 135-7.

14. Varghese JC, Liddell RP, Farrell MA, Murray FE, Osborne DH, Lee MJ. Diagnostic accuracy of magnetic resonance cholangiopancreatography and ultrasound compared with direct cholangiography in the detection of choledocholithiasis. Clin Radiol. 2000; 55(1): 25-35. Erratum in: Clin Radiol 2000; 55:657.

15. Becker CD, Grossholz M, Mentha G, Peyer R, Terrier F. MR cholangiopancreatography: technique, potential indications, and diagnostic features of benign, postoperative, and malignant conditions. Eur. Radiol. 1997; 7(6): 865-74.

16. Maurea S, Caleo O, Mollica C, Imbriaco M, Mainenti PP, Palumbo C, et al. Comparative diagnostic evaluation with MR cholangiopancreatography, ultrasonography and CT in patients with pancreatobliary disease. Radiol Med. 2009; 114(3): 390-402.

Correspondence to/Autor za korespondenciju
Turgay Kara, MD
Address: Konya Eğitimve Araştırma Hastanesi, Radyoloji Bölümü
Hacı Şaban Mah, Meram Yeni Yol Caddesi, No: 97
PC: 42090, Meram, Konya, Türkiye
Telephone: +90 5055197559
Fax: +90332 323 67 23
E-mail: trgykr@gmail.com.tr

SANAMED
2019; 14(2): 185–190
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i2.311
UDK: 616.34-007
ID: 278331148
Case report

UNCOMMON INTESTINAL MALROTATION IN ADULT PATIENTS - PRESENTATION OF 4 CASES

Muhammedoglu Bahtiyar,[1] Topuz Sezgin,[2] Saracoglu Mustafa,[3]
Koktas Suleyman,[2] Pircanoglu Eyup Mehmet,[2] Kara Turgay[4]

[1] Department of Gastroenterologic Surgery, Necip Fazsl State Hospital, Kahramanmaras, Turkey
[2] Department of Surgery, Necip Fazıl State Hospital, Kahramanmaras, Turkey
[3] Department of Gastroenterologic Surgery, University of Health Science,
Konya Trainning and Research Hospital, Konya, Turkey
[4] Department of Radiology, University of Health Science,
Konya Trainning and Research Hospital, Konya, Turkey

Primljen/Received 28. 01. 2019. god.
Prihvaćen/Accepted 16. 04. 2019. god.

Abstract: Rotation anomalies are usually anomalies seen in children. It is a rare condition in adults. In this article, 4 cases are presented. In the first case, reverse rotation anomaly and appendicitis perforation were detected in a patient who had laparotomy at the age of 22 with acute abdomen. It is a unique condition that the patient had a history of previous appendectomy. Ladd band may be the cause of acute abdomen due to ileus. The patient in our second case presented a concurrent biliary stone and malrotation with Ladd band. In addition, two elderly patients who underwent hemicolectomy due to intestinal ileus caused by malrotation were presented with literature review.

Key words: Midgut, Intestinal Malrotation, Volvulus, Imaging, Surgery.

INTRODUCTION

Any failure in normal embryological 270° counter clockwise intestinal rotation around the superiormesenteric vessels is considered to be malrotation. Duodenum and jejunum is situated on the rightside of columna vertebralis in these patients. This anomaly causes intermittent episodes of acute events such as gastrointestinal obstruction or volvulus (1). Midgut malrotation occurs in about 1 out of 500 newborns. The incidence of intestinal malrotation in adults is about 0.2% (2). Asymptomatic cases are usually diagnosed coincidentally during another surgery. The presence of narrow mesenteric root with a long pedicle and having a mobile colon segment are among the predisposing factors (3, 4, 5). 6% of the neonatal obstruction is caused by rotation anomalies (6). Rotation anomalies seen in the large intestine most commonly affects the sigmoid colon as 40% (7). Peritoneal bands are often associated with intestinal malrotation and divided to 4 types. In type 1; there is an abnormal band extending from the caecum to the right upper quadrant and crosses the 2nd and 3rd parts of the duodenum and compresses to the duodenum. This is called Ladd's band (8).

Double-contrast enhanced computed tomography (CT), magnetic resonance imaging (MRI), angiography and sometimes diagnostic laparotomy are used for diagnosis. Diagnostic laparoscopic imaging is indicated for patients with intestinal malrotation in case of upper gastrointestinal system uncertainty.

Treatment of intestinal malrotation was first described in 1936 by William E. Ladd, the great pediatric surgeon in North America, and is currently the basis for malrotation therapy (9). Open Ladd's Procedure consists of, transverse incision or midline laparotomy, evisceration of intestinal contents, detorsion counter-clockwise if volvulus is present, resection grossly necrotic bowel, consideration second look laparotomy if questionable viability, releasing of Ladd's cecal bands, broadening the small intestine mesentery, profilactic appendectomy, placement small bowel on right and colon on left (9). Laparoscopic Ladd procedure is a technique applied for intestinal malrotation in adults in order to eliminate chronic symptoms (9). As a less invasive and cosmetically attractive technique, the use of single-incision laparoscopic surgery (SILS) have increased. The expected advantages SILS include less pain, recovery time, and less trocar injury rates (10, 11, 12).

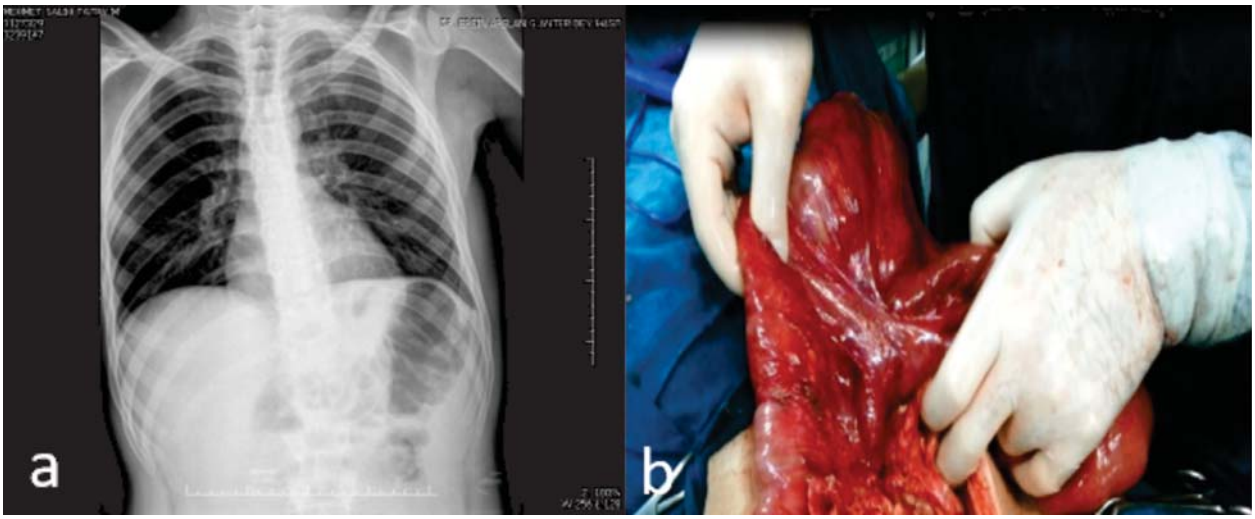


Figure 1. *a) X ray shows large bowel on left part of abdomen b) Patient's ladd operation was performed. Mesenteric root was detorsioned*

We present four cases of adult malrotation who presented with chronic abdominal pain and/or ileus.

CASE 1

A 22-year-old Syrian male, who had an appendectomy operation history 1 week ago abroad, admitted to the emergency department of the public hospital. The pain continued after the appendectomy operation. In physical and laboratory examinations, colonic obstruction findings and lokocytosis were detected. Ultrasonography (US) revealed free fluid in the abdomen. Plain radiography of abdomen revealed large bowels clustering on left (Figure 1a). The patient was considered to have secondary adhesions and ileus. Laparotomy was decided due to acute abdomen findings. During the operation, it was seen that all the loops between treitz ligament and sigmoid colon turned on theirselves and the mesenteric circulation was disrupted. It was seen that the cecum was atypically in the left lower quadrant and duodenojejunal junction was on the right side of abdomen. Appendix had not been taken and was perforated from the tip. Abdomen was looking infected and dirty All the small intestines were volvulized and edematous and hyperemic. It was considered as complete nonrotation anomaly. The patient underwent open Ladd's operation; bowel loops were detorsed in a counterclockwise direction and Ladd bands which are crossing from right paracolic area to the right colon and cecum were lysed. Blood flow in the mesentery was checked. There was no blood flow impairment. Appendectomy was performed (Figure 1b). The bowel loops were replaced. At the end of operation small bowel loops were in the right abdomen and the cecum and other colon segments were in the left abdomen. The postoperative period was uneventful.

CASE 2

A 59-year-old female patient was admitted to the hospital with abdominal pain, intermittent nausea, vomiting and jaundice for 1 week. Pain has been present for 5-6 years, but recently the severity and frequency of attacks have increased gradually. On physical examination, there were no signs of abdominal distention. In abdominal US, cholelithiasis and choledocholithiasis were observed and magnetic resonance cholangiopancreatography (MRCP) was recommended. In the MRCP, the common bile duct was 2 cm wide and 1.5 cm stone was observed in the lumen (Figure 2a, 2b). Direct abdominal radiography and chest radiography were normal. Because the patient was managed with the diagnosis of cholelithiasis and choledocholithiasis, abdominal tomography was not requested. Since the view was primarily compatible with choledocholithiasis, Endoscopic Retrograde Cholangio-Pancreatography (ERCP) was planned to the patient. Since the stone was 1.5 cm, the ERCP procedure was determined as a "difficult stone" and the open surgical consent form was signed for the possibility of failure of the procedure. Although sphincterotomy and endoscopic papillary large balloon dilation (ELBD) were performed in ERCP, stone could not be removed. Cholangiography confirmed the 1.5 cm stone in common bile duct (choledoch). In this case, open surgery decision was taken. The right subcostal incision (Kocher's) was used to enter into the abdomen. The small bowel was located on the right and the large intestine was located on the left. A fibrotic band, Ladd band, extending from the subhepatic area compressing to the duodenum was observed. The diagnosis was complete nonrotation anomaly. The common bile duct was dilated over 2 cm. Choledochotomy, choledochoduodenostomy, cholecystectomy and

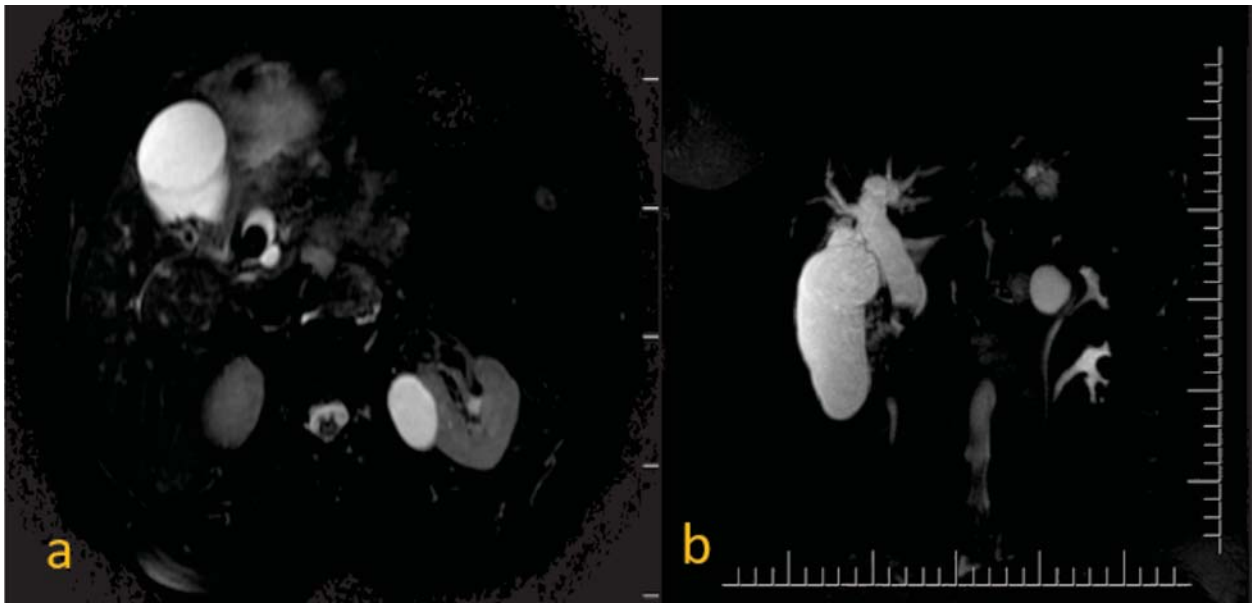


Figure 2. *MRCP shows stone in common bile duct a) axial b) coronal view*

Ladd band excision were decided. The duodenum was cohered and the Ladd band over the duodenum was excised. Cholecystectomy and choledochoduodenostomy were performed. The bowel loops were left in original malrotated positions. The small intestine was placed on the right and the large intestine was placed to the left and a drain was placed in the subhepatic area and the operation was terminated. The postoperative period was uneventful.

CASE 3

A seventy-four-year-old female patient was admitted to the emergency room with abdominal pain, intermittent nausea, vomiting and jaundice in the last 2 weeks. She had abdominal distention and epigastric defense. She had occasionally abdominal pain and vomiting on medical history. Abdominal x-ray showed that the right colon was on the left half of the abdomen (Figure 3a). Leukocytosis, mild increased total and direct bilirubin and electrolyte imbalance were seen on labarotory test. Laparotomy was performed with the diagnosis of ileus. At exploration the cecum was malrotated, in left upper quadrant. But duodenojejunal junction was in the original place. Treitz ligament was formed as usual. The cecocolic malrotation was diagnosed. The mesenteric root was volvulized and purple in color consistent with ischemia. When right colon and ileal segments were detorsed in a counterclockwise direction Ladd's band was seen over hepatic flexure, that crossing from right retroperiton to the cecum, which is in the left upper abdomen. Ladds procedure was applied to the patient (Figure 3b). After detorsion of mesentery, the color of the midgut colon didn't changed and necrosis was diagnosed. Therefore exten-

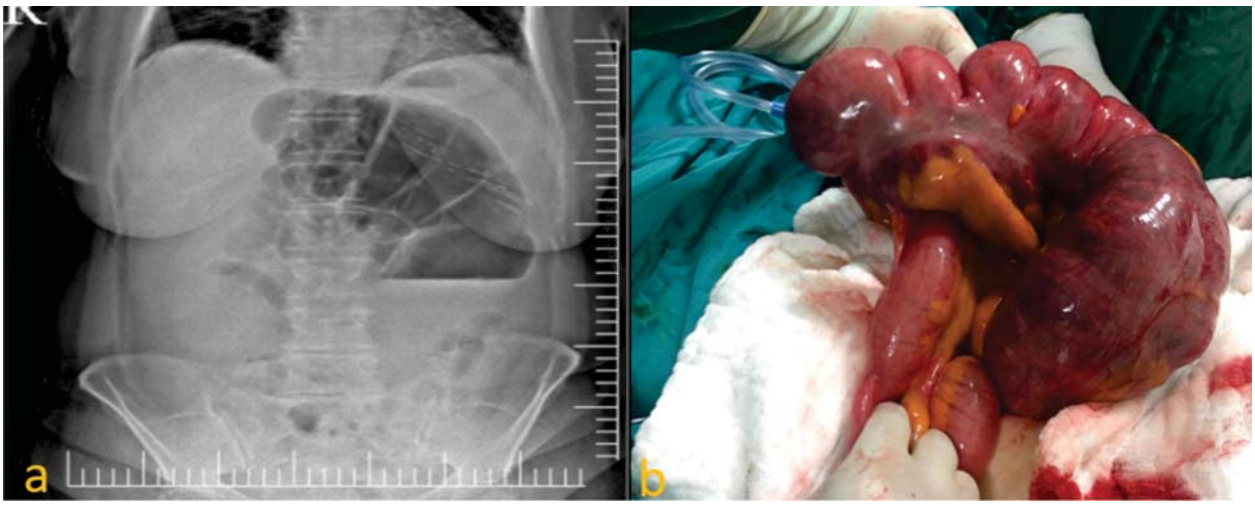


Figure 3. *X ray, colon was on the left half of the abdomen. b) Ladd's Procedure, detosion of mesenteric root which seemed ischemic*

ded right hemicolectomy was performed. The postoperative period was uneventful and she was discharged on postoperative day 9th.

CASE 4

A 84-year-old female patient was admitted to the emergency department of the public hospital. She had abdominal pain for 1 week and fecaloid vomiting. She had fever, hypotension and tachycardia on physical examination, consisting with sepsis. On laboratory test leukocytosis, mild anemia and electrolyte imbalance were seen. Findings of colonic obstruction were detected in the examinations. US revealed free fluid in the abdomen. Computed Tomography (CT) revealed enlarged intestinal loops with air-fluid levels (Figure 4). Acute laparotomy decision was settled because of acute abdomen findings. During the operation, it was observed that all the loops between the Treitz and sigmoid colon had turned on itself and the circulation of the mesentery was disrupted. Bowel loops were volvulized. It was seen that the caecum was in the lower left quadrant. The small bowel segments were in the right abdomen. Complete nonrotation anomaly was considered.

Infected fluid was seen in the abdomen. All the small intestines were edematous and hyperemic. The patient underwent Ladd's procedure operation. The root of the mesentery was derotated by turning counterclockwise. Blood flow in the mesentery was checked. Serosa of the caecum was purple and blood supply was impaired. It was observed that the circulation was not improved by detorsion therefore right hemicolectomy was performed. Abdomen was washed, the drain was placed and closed. The postoperative period was uneventful and she was discharged.

DISCUSSION AND CONCLUSION

Intestinal malrotation is considered a rare entitiy in adults. But Durkin et al (13) pointed out that intestinal malrotation in adults is diagnosed almost as often in adults as in children. Also it has a diagnostic dilemma in adulthood. Adult patients with intestinal malrotation can present with acute and chronic clinical conditions. Patients seek remedy for diverse non-specific complaints such as vague abdominal cramps, nausea, emesis, intermittent diarrhea, hematochezia, constipation and weight loss. Patients with these chronic non-specific symptoms apply to hospitals frequently but it takes a long time to make a true diagnosis. A high index of clinical suspicion is necessary. On occasions adult patients with rotation anomaly can present with abdominal catastrophe such as midgut volvulus, intestinal ischaemia and gangrene. So general surgeons should become familiar with intestinal malrotation symptoms and its treatment.

It is suggested that the gold standart imaging modalities for diagnosis of intestinal malrotation are upper gastrointestinal (UGI) contrast series and CT imaging with oral and IV contrast agent. UGI is suitable for children. In adult patients typical findings of CT scans are reversed relation of superior mesenteric artery (SMA) and superior mesenteric vein (SMV), whirlpool sign, small bowel loops in the right abdomen, a lack of visualization of ceacum in the right iliac fossa, dilatation of various duodenal loops and duodenojejunal loops to the right (corkscrew sign).

Treatment of intestinal malrotation was first described in 1936 by William E. Ladd, the great pediatric surgeon in North America, and is currently the basis for malrotation therapy (9). Open Ladd's Procedure consists of, transverse incision or midline laparotomy,

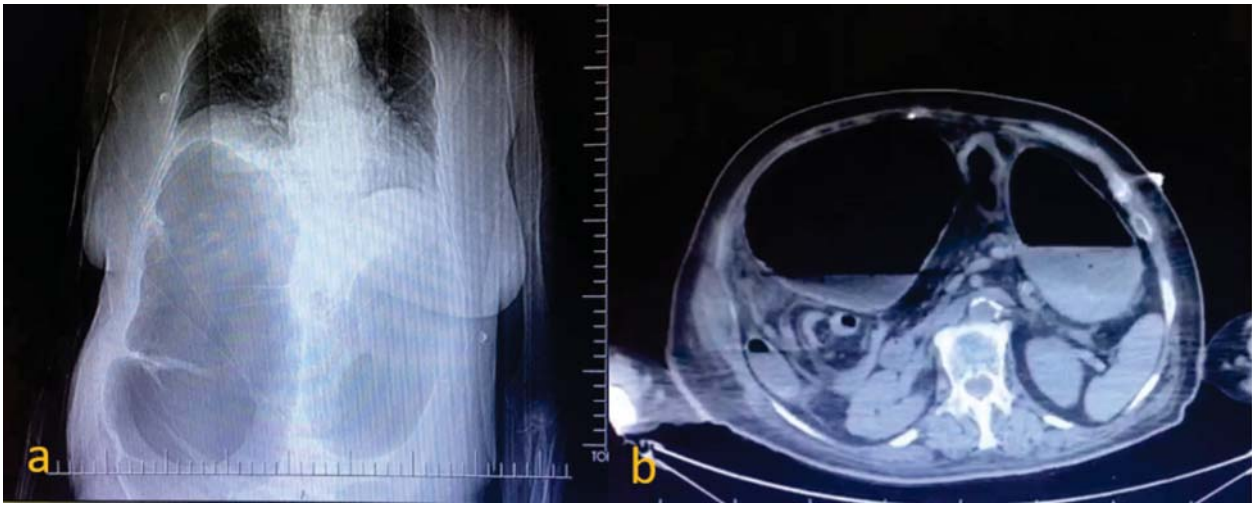


Figure 4. *a) Abdomen X ray shows caecum in the lower left quadrant and enlarged colon segments on right. b) contrast enhanced-CT revealed enlarged intestinal loops with air-fluid levels*

evisceration of intestinal contents, detorsion counter-clockwise if volvulus is present, resection grossly necrotic bowel, consideration second look laparotomy if questionable viability, releasing of Ladd's cecal bands, broadening the small intestine mesentery, profilactic appendectomy, placement small bowel on right and colon on left (9). Also laparoscopic Ladd procedure is a technique applied for intestinal malrotation in adults in order to eliminate chronic symptoms.

Our cases draw attention by several points. Three of four patients were diagnosed with complete nonrotation anomaly, the most common presentation. The remaining rotation anomaly was isolated isolated cecocolic malrotation.

In our first case, a 22-year-old patient who underwent laparotomy with the diagnosis of acute abdomen, had complete nonrotation anomaly and appendicitis perforation. It is a unique condition that the patient had a history of previous appendectomy. Whatever the patient's anamnesis, the suspicious approach has always been life-saving.

As is known in the literature, Ladd bands may be the cause of acute abdomen due to ileus. In our second case, a gallstone was found in the gallbladder accompanying Ladd band. Did the Ladd band cause choledocholithiasis as a result of chronic obstruction of the duodenum and common bile duct or was it incidental? The presence of ladd bands may lead to compression of the duodenum, small bowel; volvulus, ischemia and necrosis. The presentation is difficult due to rarety in the elderly. According to the literature, most of the patients were treated by laparotomy and only a few cases were operated laparoscopically (10). John Vassaur et al. claimed that the SILS technique in the intestinal malrotation is successful and reliable when performed by an experienced surgeon (11). According to the study of Lodwick et al. patients who underwent laparoscopic Ladd procedure had short hospital stay and a decrease rate in complications such as bowel obstruction, but post-surgical volvulus incidence increased (12). It has not been established that small bowel fixation in operation prevents the volvulus in patients with intestinal malrotation. In the pediatric series, this complication occurs between 10-15% of cases after Ladd procedure.

In conclusion, eventhough the use of preoperative imaging modalities helps to diagnose the rare reasons of intestinal malrotation, sometimes the diagnosis is made only during surgery. The Ladd's procedure is safely performed in the surgical treatment of intestinal malrotation. After the Ladd process, the intestines should be left in place. Ileus is a known complication of intestinal malrotation. In case 2, did Ladd band cause choledocholithiasis as a result of chronic obstruction of the duodenum and common bile duct or is it incidental? We can find the answer to this question by following other case reports.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Licensing

Sažetak

NEUOBIČAJENA CREVNA MALROTACIJA KOD ODRASLIH PACIJENATA - PRIKAZ 4 SLUČAJA

Muhammedoglu Bahtiyar,[1] Topuz Sezgin,[2] Saracoglu Mustafa,[3]
Koktas Suleyman,[2] Pircanoglu Eyup Mehmet,[2] Kara Turgay[4]

[1] Department of Gastroenterologic Surgery, Necip Fazsl State Hospital, Kahramanmaras, Turkey
[2] Department of Surgery, Necip Fazıl State Hospital, Kahramanmaras, Turkey
[3] Department of Gastroenterologic Surgery, University of Health Science, Konya Trainning and Research Hospital, Konya, Turkey
[4] Department of Radiology, University of Health Science, Konya Trainning and Research Hospital, Konya, Turkey

Rotacione anomalije su obično anomalije koje se sreću kod dece. To je retko stanje kod odraslih. U ovom radu su prikazana 4 slučaja. U prvom slučaju, anomalija obrnute rotacije i perforacija apendiksa otkriveni su kod pacijenta koji je imao laparotomiju u dobi od 22 godine sa znacima akutnog abdomena. To je jedinstven slučaj da je pacijent imao istoriju prethodne apendektomije. Ladova priraslica može biti uzorok akutnog abdomena zbog ileusa. Pacijent je u našem drugom slučaju imao bilijarnu kalkulozu i malrotaciju sa Ladovom priraslicom. Pored toga, dva starija pacijenta koja su bila podvrgnuta hemikolektomiji usled crevnog ileusa izazvanog malrotacijom, prikazana su u pregledu literature.

Ključne reči: srednje crevo, intestinalna malrotacija, Volvulus, operacija.

REFERENCES

1. Haak BW, Bodewitz ST, Kuijper CF, de Widt-Levert LM. Intestinal malrotation and volvulus in adult life.. Int J Surg Case Rep. 2014; 5(5): 259–61.

2. Sheikh F, Balarajah V, Ayantunde AA. Recurrent intestinal volvulus in midgut malrotation causing acute bowel obstruction: A case report. World J Gastrointest Surg. 2013; 5(3): 43-6.

3. Gunsar C, Karaca I, Sencan A, Ceylan H, Mir E. Clinical presentation and radiographic identification of intestinal rotation anomalies in symptomatic neonates. Journal of the Turkish Association of Pediatric Surgeons. 2002; 16(1): 12-5.

4. Ford EG, Senac MOJr, Srikanth MS, Weitzman JJ. Malrotation of the intestine in children. Ann Surg.1992; 215(2): 172-8.

5. Powell DM, Othersen HB, Smith CD. Malrotatiton of the intestine in chidren. The effect of age on presentatiton and therapy. J.Pediatr Surg.1989; 24(6): 777-80.

6. Stockmann PT. Maltoration. In: Oldham KT, Colombani PM, Foglia RP, Skiner MA. Principles and practice of pediatric surgery.(editörden). Philadelphia: Lippincott Williams and Wilkins, 2005: 1283-96.

7. Yaseen ZH, Watson RE, Dean HA, Wilson ME.. Case report: transverse colon volvulus in a patient with Clostridium difficle pseudomembranous colitis. Am J Med Sci. 1994; 308(4): 247-50.

8. Tanrıkulu Y, Tanrıkulu CS, Temiz A, Karaman S, Akalp SO. Intestinal malrotation in an adult patient. Yeni Tıp Derg. 2014; 31(2): 125-7.

9. Panda N, Bansal NK, Narasimhan M, Ardhanari R. Laparoscopic correction of intestinal malrotation in adult. J Minim Access Surg. 2014; 10(2): 90-2.

10. Bimbaum DJ, Geffroy Y, Goin G, Balandraud P. Left side appendicitis with midgut malrotation in an adult. J Surg Tech Case Rep. 2013; 5(1): 38–40.

11. Vassaur J, Vassaur H, Buckley FP. Single-Incision laparoscopic Ladd's procedure for intestinal malrotation JSLS. 2014; 18(1): 132-5.

12. Lodwick DL, Minneci PC, Deans KJ. Current surgical management of intestinal rotational abnormalities. Curr Opin Pediatr. 2015; 27(3): 383-8.

13. Durkin ET, Lund DP, Shaaban AF, Schurr MJ, Weber SM. Age related differences in diagnosis and morbidity of intestinal malrotation. J Am Coll Surg. 2008; 206 (4): 658-63.

Correspondence to/Autor za korespondenciju
Turgay Kara
Department of Radiology, University of Health Science, Konya Trainning and Research Hospital, Konya, Turkey
email: attrgykr@gmail.com

SANAMED
2019; 14(2): 191–194
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i2.326
UDK: 616.5-006.81; 616.366-006-033.2
ID: 278336524
Case report

METASTATIC CUTANEUS MELANOMA OF THE GALLBLADDER - CASE REPORT

Prgova Veljanova Biljana,[1] Nancheva Bogoevska Andrea,[1] Bozinovska Beaka Gordana,[2] Gjoreski Aleksandar,[1] Nancheva Jasminka[3]

[1] Department of diagnostic and interventional radiology, City General Hospital 8th September - Skopje, Macedonia
[2] Department of general surgery, City General Hospital 8th September - Skopje, Macedonia
[3] Department of orthopedic surgery, Medicalfaculty, Ss. Cyril and Methodius University - Skopje, Macedonia

Primljen/Received 25. 03. 2019. god. Prihvaćen/Accepted 17. 06. 2019. god.

Abstract: Melanoma is an aggressive malignant tumor that originates from melanocytes and most commonly occurs on the skin. Dominantly metastasize to regional lymph nodes, in the brain and lungs and rarely in the gastrointestinal (GI) system. The aim of this report is to present a rare case of metastasis of cutaneous malignant melanoma in the gallbladder, discovered 10 months after excision of the primary melanoma of the skin. A 45-year-old patient was hospitalized in our hospital due to abdominal pain in right upper quadrant and nausea lasting for 7 days. An intraluminal substrate was found in the gallbladder with computed tomography and later a CT guied biopsy was performed on it, thus proving a metastatic deposit of primary malignant melanoma.

Metastatic deposits in the gallbladder are extremely rare finding, and 238 cases have been described in the literature.

Key words: malignant melanoma, mestastases, CT, biopsy, gallbladder.

INTRODUCTION

Cutaneous melanoma is an aggressive disease, which arises from melanocytes, a type of cells found in the epidermis, uvea, meninges, intestinal tract, upper respiratory tract, and the regional lymph nodes. Statistically is less than 5% of all skin cancer cases, but it has extremely high morbidity and mortality due to its high tendency to metastàsize throughout the body (1–4). Common sites of metastases are the lungs, brain, liver, and GI tract (1–3). In 2–4% of patients with cutaneous melanoma that are diagnosed with gastrointestinal metastases, mostly affected parts are small bowel, colon, and stomach (1, 2). Metastatic involvement of the gallbladder is rare, and is often part of a complex of metastases in other parts of the body with a very poor prognosis and non-specific symptoms. According to recent literature data - there is an increased number of patients with diagnosed skin melanoma that metastasized in the gallbladder.

In this article, we present a rare case of melanoma metastasis in the gallbladder following cutaneous melanoma operative treatment. A patient was admitted in our emergency unit with right upper quadrant abdominal pain and nausea lasting for 7 days. Palliative therapy was administered; radiological examination and laboratory tests were performed as well as biopsy. Because of complications from other organs failure the patient past away after four weeks.

CASE REPORT

Written consent for publishing medical data for the above-mentioned patient was obtained from his family. We present a 45-year-old male with a medical history of cutaneous melanoma of the back, admitted to the hospital with strong abdominal pain in the right upper quadrant and persistent nausea that started 7 days ago. Ten months prior to this admission, the patient was diagnosed with a nodular malignant melanoma in his left suprascapular region, Breslow thickness 11.5 mm, invasive to Clark anatomic level IV. It was done a local excision with broader margins with a negative sentinel node biopsy at the time. After the intervention he started with radiation therapy and continued with immunotherapy (interferon). The patient did not tolerate the oncologic therapy and it was incompletely finished. Contrast- enhanced computed tomography (CT) examinations of the head, thorax, and abdomen after

the intervention did not show signs of any distant metastasis. After nine months of surgery, the patient was admitted at the hospital with worsened general condition with neurological outbursts. Brain metastases were confirmed by CT. After four weeks, the patient was admitted at the hospital with the a forementioned symptoms. Staggering the blood count and metabolic panel was not significantly increased or reduced. An abdominal ultrasound showed 2 x 1 cm multiple gallbladder lesions with high blood flow on Doppler, later abdominal computed tomography (CT) confirmed it (Figure 1). Additionally brain CT and MRI were performed as well as chest CT (Figure 2, 3), all three trials showed multiple metastases. Due to his condition, the patient was not operated but was made a CT-guided core biopsy of the lesions in the gallbladder. Pathology confirmed metastatic melanoma of the gallbladder. The patient was given therapy to relieve the abdominal pain and nausea, four weeks later he passed away from complications.

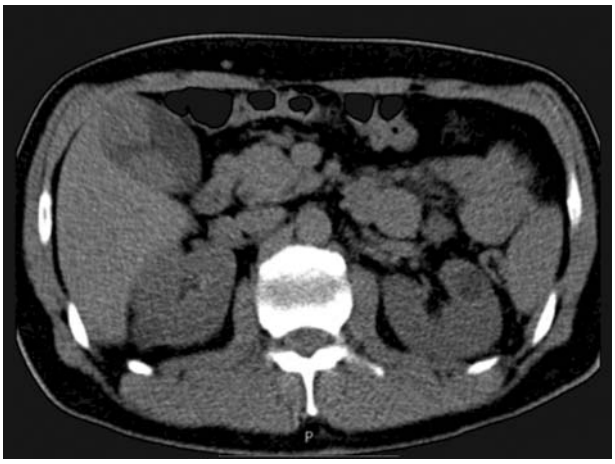


Figure 1. *Abdominal CT scan with gallbladder metastases*

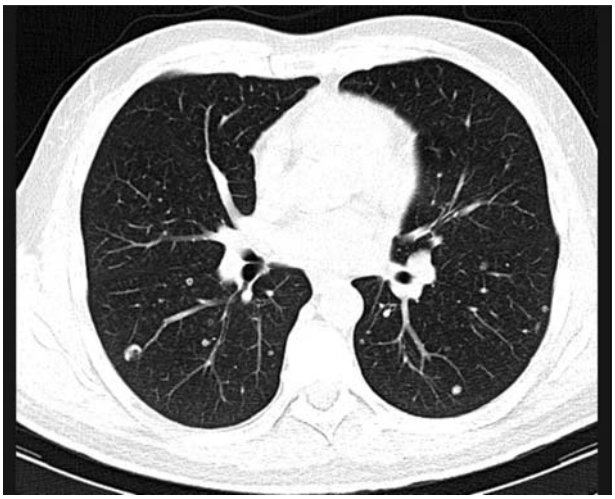


Figure 2. *Chest CT scan with multiple metastases*

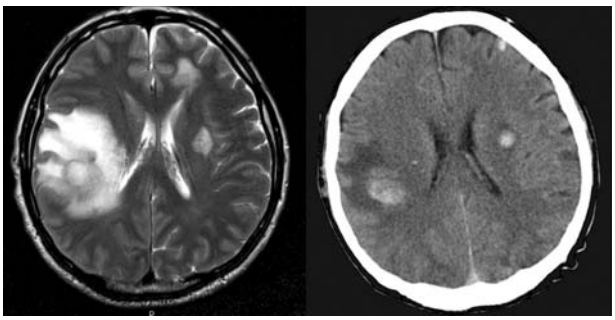


Figure 3. *MRI and CT scan with multiple metasases*

DISCUSSION AND CONCLUSION

Melanoma is cancer, which originates from melanocytes-dendritic type cells, which provides melanin to keratocytes and they can be found in most visceral organs (5). This type of malignancy represents less then 5% of all skin cancers (5), and is associated with high mortality and potential for wide metastatic spread. As soon as metastatic disease occurs, the prognosis is very poor with a mean survival rate of approximately 8.4 months (6). When melanoma stars to spread, it penetrates first the local lymph vessels and hematogenous to more distant sites like lungs (50-75%), liver (54-77%), and brain (7). Patients diagnosed with skin melanoma have rear GI metastases only 2-4% (8), most common sites for GI metastases are small bowel (35-65%), colon (5-9%) and stomach (5-7%) (1, 2). Cutaneous metastatic melanoma to the gallbladder is rarely found during patients life, 5-year survival is reported in only 15% of the diagnosed (9), that's why most of the statistics come from autopsy reports that range the incidence of this metastatic disease from 15 to 20% (10). Most patients are asymptomatic, the symptoms occur when the disease is widespread (11). On the other site, there is a small group of patients with acute cholecystitis, bile duct obstruction as well as hemobilia and fistulas that give an early presentation of this type of metastases. (12, 13). Abdominal ultrasound and Doppler ultrasound showed presence of a gallbladder malignancy by detecting high blood flow in that region (single or multiple infiltrative lesions at least 1cm in diameter attached to the inner mucosal wall). With that they are first modalities of choice for evaluation of gallbladder lesions (14). Secondly comes CT (2), and last biopsy with immune histochemical staining as final step to confirm the diagnosis (2). Positron emission tomography is used to detect the extent of disease spread. Surgery as a treatment for metastatic melanoma to the gallbladder is arguable since most of the cases are already with widespread disease (1). Metastasectomy is considered for palliative and symptom-reducing effects approach in cases of a single localized lesion to the gallbladder and also as a preven-

tion of further spreading of the disease ,with 1-year survival postoperatively (1, 3). Sometimes a liver wedge resection is needed to avoid spreading of neoplastic cells (1, 3). High survival rates are seen in patients that are treated with chemoimmunotherapy with widespread/non-localized disease (1, 3). The chemoimmunotherapy includes use of high-bolus interleukin-2(IL-2), with its limitation in use due to toxicity (1, 3). Along this therapy BRAF inhibitors are used, but their effectiveness is demonstrated with the parallel use of MEK inhibitors, which results with lower adverse reactions and prolong disease free-survival, compared to isolated use of BRAF inhibitors (1, 3). As conclusion good treatment can be achieved with laparoscopic cholecystectomies and/or chemoimmunotherapy.This case report was presented in order to teach us to make more prompt workup of potential metastases in patients with diagnosed cutaneous melanoma.

Acknowledgment: None

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Licensing

Sažetak

METASTAZA KUTANOG MELANOMA U ŽUČNU KESU - PRIKAZ SLUČAJA

Prgova Veljanova Biljana,[1] Nancheva Bogoevska Andrea,[1] Bozinovska Beaka Gordana,[2] Gjoreski Aleksandar,[1] Nancheva Jasminka[3]

[1] Department of diagnostic and interventional radiology, City General Hospital 8th September - Skopje, Macedonia
[2] Department of general surgery, City General Hospital 8th September - Skopje, Macedonia
[3] Department of orthopedic surgery, Medicalfaculty, Ss. Cyril and Methodius University - Skopje, Macedonia

Melanom je agresivni maligni tumor koji potiče od melanocita i najčešće se javlja na koži. Dominantno metastazira u regionalne limfne čvorove, mozak, pluća, a ređe u gastrointestinalni sistem. Cilj ovog rada jeste da prikaže redak slučaj metastaziranja kožnog melanoma u žučnu kesu, otkrivenog 10 meseci nakon uklanjanja primarnog melanoma kože. Pacijent starosti 45 godina je hospitalizovan u našoj bolnici zbog bolova u trbuhu u predelu desnog gornjeg kvadranta i mučnine u trajanju od sedam dana. Intraluminalni supstrat je kompjuterskom tomografijom, a kasnije i CT biopsijom pronađen u žučnoj kesi, čime je dokazano metastatsko taloženje primarnog malignog melanoma. Metastatske naslage u žučnoj kesi su izuzetno redak nalaz, a u literaturi je opisano 238 slučajeva.

Ključne reči: maligni melanom, metastaze, CT, biopsija, žučna kesa.

REFERENCES

1. Giannini I., Cutrignelli D. A., Resta L., Gentile A., Vincenti L. Metastatic melanoma of the gallbladder: report of two cases and a review of the literature. Clin Eco Med. 2016; 16(3): 295–300.

2. Ettahri H., Elomrani F., Elkabous M., Rimani M1, Boutayeb S1, Mrabti H et al. Duodenal and gallbladder metastasis of regressive melanoma: a case report and review of the literature. J Gastrointestin Oncol. 2015; 6(5): E77–E81.

3. Haskaraca M. F., Ozsoy M., Özsan ¤., Kurt K. Primary malignant melanoma of the gallbladder: a case report and review of the literature. Case Rep Surg. 2012; 2012: 693547.

4. Cellerino P., Corsi F., Morandi E., Foschi D., Trabucchi E. Metastatic melanoma of the gallbladder. Eur J Surg Onco 2000; 26(8): 815–6.

5. Samplaski MK, Rosato EL, Witkiewicz AK, Mastrangelo MJ, Berger AC. Malignant melanoma of the gallbladder: a report of two cases and review of the literature. J Gastrointestinal Surge. 2008; 12(6): 1123–6, 2008.

6. Guida M, Cramarossa A, Gentile A, Benvestito S, De Fazio M, Sanbiasi D et al. Metastatic malignant melanoma of the gallbladder: a case report and review of the literature. Melanoma Res. 2002; 12(6): 619–25.

7. Gogas J., Mantas D., Gogas H., Kouskos E., Markopoulos C., Vgenopoulou S. Metastatic melanoma in the gallbladder: report of a case. Surg Today. 2003; 33(2): 135–7.

8. Christou D., Katodritis N., Decatris MP. Katodritou A, Michaelides I, Nicolaou N et al. Melanoma of the gallbladder: appropriate surgical management and review of the literature. Clin Case Rep. 2014; 2(6): 313–8.

9. Dong XD., DeMatos P., Prieto VG., Seigier HF. Melanoma of the gallbladder: a review of cases seen at Duke University Medical Center. Cancer. 1999; 85(1): 32–9.

10. Nelson RS, Lanza F. Malignant melanoma metastatic to the upper gastrointestinal tract: endoscopic and radiologic correlations, form and evolution of lesions, and value of directed biopsy in diagnosis. Gastrointestinal endoscopy. 1978; 24(4): 156-8.

11. Cellerino P, Corsi F, Morandi E, Foschi D, Trabucchi E. Metastatic melanoma of the gallbladder. Eur J Surg Oncol. 2000; 26(8): 815-6.

12. Vernadakis S, Rallis G, Danias N, Serafimidis C, Christodoulou E, Troullinakis M et al. Metastatic melanoma of the gallbladder: an unusual clinical presentation of acute cholecystitis. World J Gastroenterol. 2009; 15(27): 3434–6.

13. Daunt N, King DM. Metastatic melanoma in the biliary tree. Br J Radiol. 1982; 55(659): 873-4.

14. Guida M, Cramarossa A, Gentile A, Benvestito S, De Fazio M, Sanbiasi D et al. Metastatic malignant melanoma of the gallbladder: a case report and review of the literature. Melanoma Res. 2002; 12(6): 619–25.

Correspondence to/Autor za korespondenciju
Nancheva Bogoevska Andrea
Department of diagnostic and interventional radiology,
City General Hospital 8th September - Skopje, Macedonia
email: andrea.nanceva@gmail.com

SANAMED
2019; 14(2): 195–198
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i2.335
UDK: 616.25-003.2
ID: 278329868
Case report

TUBERCULOUS PLEURAL EFFUSION IN THE PREVIOUSLY HEALTHY MAN - CASE REPORT AND REVIEW OF THE LITERATURE

Lazovic Biljana,[1] Blazic Ivana,[1] Detanac Dzemail,[2] Milic Rade,[3] Sarac Sanja,[3] Detanac Dzenana,[2] Zugic Vladimir[4]

[1] University clinical center "Zemun", Belgrade, Serbia
[2] General Hospital Novi Pazar, Serbia
[3] Military Medical Academy, Clinic for pulmonology, Belgrade, Serbia
[4] Clinic for lung diseases, Clinical center of Serbia, Belgrade, Serbia, University of Belgrade, Serbia

Primljen/Received 26. 05. 2019. god. Prihvaćen/Accepted 17. 06. 2019. god.

Abstract: **Introduction:** Although pleural effusion is a common clinical manifestation, the differential diagnosis of the cause of the pleural effusion is often challenging, especially in the early differentiation of tuberculous pleurisy (TP) from other pleural effusion.

Case report: We present a previously healthy man who had no contagious or TB contact but developed massive tuberculous pleural effusion which eventually was unexpected tuberculous. He started with therapy per protocol and feeling well. The purpose of this case and review of literature was to remind the physicians that tuberculosis is not a sickening illness, but on the contrary, it is in the expansion.

Discussion: When a patient presents with new pleural effusion, the diagnosis of tuberculous pleuritis should be considered. The patient is at great risk for developing pulmonary or extra pulmonary TB if the diagnosis is not made properly. Between 3% and 25% of patients with TB will have TB pleuritic or more in immunocompromised patients.The treatment for TB pleuritis is the same as that for pulmonary TB.

Conclusion: The gold standard for the diagnosis of tuberculous pleural effusion remains the detection of Mycobacterium tuberculosis in pleural fluid, or pleural biopsy specimens, either by microscopy and/or culture, or the histological demonstration of caseating granulomas in the pleura along with acid fast bacilli.

Key words: effusion, pleuritic pain, pleurisy, pleural biopsy, TBC, treatment.

INTRODUCTION

Tuberculosis accounts for millions of active disease cases and deaths in both developed and developing countries (1). The proportion of patients with tuberculosis who have pleural effusions has varied markedly from population to population (1, 2). Tuberculous pleural effusion occurs in approximately 5% of patients with Mycobacterium tuberculosis (TB) infection and accounts for 4% of all TB cases in the United States (2). Diagnosis is challenging, with 48-96% of tuberculous pleural effusions negative by sputum acid-fast bacilli (AFB) stain and culture (3, 4). Thoracentesis is frequently performed and shows an exudative, lymphocytic pleural effusion in more than 90% of cases but direct examination reveals acid-fast bacilli (AFB) in less than 10% of cases (5, 6). As AFB stain and cultures are often negative and biomarkers cannot guide therapy, more invasive diagnostic measures are usually required. The following case illustrates the clinical presentation and diagnostic approach in anatypical caseof suspected tuberculous pleural effusion, which presented typically eventuallyin a previouslyhealthy man, as well as review of literature.

CASE REPORT

A male temporary resident of Russian descent, 51 years of age, was referred by a general practitioner (GP) to our hospital because of routinely annually done chest x ray which showed left sided pleural effusion for further diagnostic. The patient reported that he is mechanical engineer who work in Serbia for 5 years in comfort surroundings. He had not traveled in the past few years.He observed that he had weight lossof 7 kilograms in last 6 months, apart from good appetite,but no shortness of breath at rest, chest pain, fevers, or sick contacts. He had never smoked. He had no infectious contacts or a history of tuberculosis (TB) or immuno-

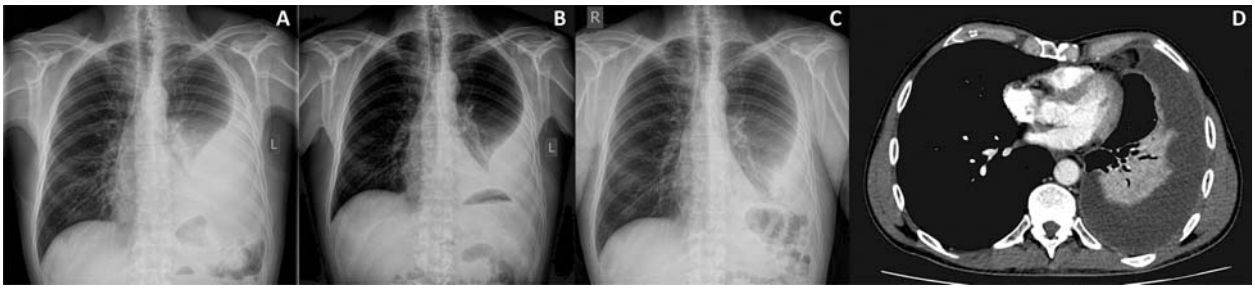


Figure 1. *A. B. C. Series of chest X rays showing left plural effusion decreasing under the treatment. D. Arterial phase of chest CT showing large pleural effusion on the left side with partial consolidation of the left lover lobe due to inflammatory changes with negative bronchogram sign*

suppression. One week prior to presentation, he was empirically treated for pneumonia with levofloxacin without improvement.

On admission the patient was afebrile, with normal blood pressure, 120/80mmHg, a heart rate of 110 beats/min, and S_{pO2} of 96% while breathing room air. Cardiac sounds were clear. Physical examination revealed dullness to percussion and decreased breath sounds throughout his lefthemithorax, with normal lung sounds on the right. She had no abdominal hepatosplenomegaly or edema of either lower limb. His white blood cell count was 12 x 10^9/Lwith 73% neutrophils and 14% lymphocytes, and platelets 460 x 10^3 cells/ml. Basic chemistry was normal, exceptC-reactive protein of 49 mg/L. A repeated chest radiograph (Figure 1A) revealed a large left pleural effusion ant it regression after thoracentesis (Figure 1 B, C). Chest computed tomographyshowed large pleural effusion on the left side with inflammatory changes in left lower lobe (Figure 1 D). Human immunodeficiency virus (HIV) test was negative. Expectorated sputum revealed 3 negative stains and cultures for acid-fast –bacillus (AFB). The Quanti-FERON-TB Gold (QFT)test was indeterminate. We have done three thoracentesis. Pleural fluid was an exudate with lymphocytic predominance in 90% of cases.A percutaneous, closed pleural biopsy was performed, using an Abrams needle, yielding 6 pieces of pleural tissue that revealed granulomatous pleuritis with focal necrosis, positive by AFB stain.

The patient was started on an anti-tuberculosis regimen (isoniazid (INH) 300 mg, ethambutol (EMB) 800 mg, rifampin (RIF) 450 mg and pyrazinamide (PZA) 1000 mg) for two months and tolerate well on first control examination. The next phase of the treatment should be INH and rifampin for 4 months. Directly observed therapy (DOT) is recommended. It is also possible to use 9-month therapy of INH and rifampin if the organisms are fully susceptible to the drug (7).

DISCUSSION

Tuberculous pleuritis usually presents as an acute or subacute illness. Symptoms are present for less than 1 week in 35% of patients and present for less than 1 month in 71% (7). The most frequent symptoms are cough (~70%), which is usually non-productive, and chest pain (~70%), which is usually pleuritic (8). Most patients are febrile, but approximately 15% will be afebrile (7, 8). They may also be dyspneic if the effusion is large. If the presentation is less acute, mild chest pain may occur with at most a low-grade fever, non-productive cough, weight loss, and malaise (9). Our patient had none of symptoms mentioned above, except weight loss, to whom he did not attribute significance due to irregular meals. He had no contagious contact.

Tuberculous pleural effusion (TPE) results from Mycobacterium tuberculosis infection of the pleura and is characterized by an intense chronic accumulation of fluid and inflammatory cells in pleural space (10). TPE is the second most common form of extrapulmonary tuberculosis and a common cause of pleural effusions in endemic tuberculosis areas. TPE is usually unilateral and can be of any size. In the studies of large number population, pleural fluid occurred only on the left side in 127 (38.1%), only on the right in 161 (48.4%), and both sides were affected in 45 (13.5%). In either unilateral or bilateral effusion, the percentages of small, moderate, and large size of pleural effusions were 20.4%, 19.2%, and 60.4%, respectively (2, 8). Approximately 20% of patients with TPE have coexisting parenchymal disease on chest radiograph. However, computed tomography scanning offers a more sensitive method and can demonstrate parenchymal disease in 40–85% of cases (11).

TPE predominates in men, with an overall male-to-female ratio of 2 : 1 (4, 12). In an epidemiological analysis from the United States, TPE occurs significantly more often than pulmonary tuberculosis among persons > 65 years old, and the mean age of patients with TPE is 49 years: about 50% were younger than 45 years and 30% were over 65 years of age. In contrast, TPE affects mainly younger individuals (mean age = 34 years) in higher tuberculosis burden areas, where primary infection accounts for a large percentage of patients with TPE (2, 13). Immunocompromised pati-

ents are more likely to develop TB than non-immunocompromised patients. Because TB pleuritis is thought to be due to delayed hypersensitivity, one might hypothesize that the percentage of immunocompromised hosts with TB with pleural effusions would be lower than in immunocompetent hosts, which is not always a case (14, 15). The incidence of tuberculosis in Serbia shows a trend of swelling and it is estimated that premature data from the Institute of Public Health from 2018 is 10, 52% of which 89% are pulmonary forms of tuberculosis (16).

The best diagnostic approach to suspected tuberculous pleuritis is debated. The yield of pleural fluid smears is 10% and of pleural fluid cultures is 25–85% (4, 17). Pleural biopsy histopathology of granulomas or (+) culture has diagnostic yields ranging from 55 to 93%. Evaluation for TB with thoracentesis plus closed pleural biopsy has a 95% sensitivity, which is roughly on par with thoracoscopy. Diagnostic modalities with highest yield are slow to show results making acute workup difficult (4, 17).

The American Thoracic Society recommends a 6-month regimen for treatment of pleural TB consisting of a 2-month period of Isoniazid (INH), Rifampin (RIF), Ethambutol (EMB) and Pyrazinamide (PZA) and followed by INH and RIF daily for 4 months (17). Corticosteroids have not reduced residual pleural thickening and are not recommended (17, 18, 19). Therapeutic thoracentesis is not discussed in the guidelines and is controversial, however it is usually performed if a patient is more than mildly symptomatic (17). Significantly less residual pleural thickening and accelerated recovery of pulmonary function has been seen in patients who received therapeutic thoracentesis for TB associated effusions (19, 20). However, other studies have concluded that residual pleural thickening is not influenced by this intervention (18, 19, 20). Other drawbacks to thoracentesis include risk of transmission to health providers, bleeding, and pulmonary injury. Anyway, it's still a subject of study and further analysis perhaps would show the real path.

CONCLUSION

The diagnosis of TB pleuritis should be considered when a patient presents with new pleural effusion. The gold standard for the diagnosis of tuberculous pleural effusion remains the detection of Mycobacterium tuberculosis in pleural fluid, or pleural biopsy specimens, either by microscopy and/or culture, or the histological demonstration of caseating granulomas in the pleura along with acid fast bacilli. If the diagnosis is not made, the patient is at risk for developing pulmonary or extrapulmonary tuberculosis.The recommended treatment for TB effusion is a regimen with Isoniazid, Rifampin, Ethambutol and Pyrazinamide for two months followed by four months of two drugs, isoniazid and rifampin.

Abbreviations

TP — tuberculous pleurisy
TB — Mycobacterium tuberculosis
AFB — acid-fast bacilli
TPE — Tuberculous pleural effusion

Acknowledgment: None

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Licensing

Sažetak

TUBERKULOZNI PLEURALNI IZLIV KOD PRETHODNO ZDRAVOG PACIJENTA - PRIKAZ SLUČAJA I PREGLED LITERATURE

Lazovic Biljana,[1] Blazic Ivana,[1] Detanac Dzemail,[2] Milic Rade,[3] Sarac Sanja,[3] Detanac Dzenana,[2] Zugic Vladimir[4]

[1] University clinical center „Zemun", Belgrade, Serbia
[2] General Hospital Novi Pazar, Serbia
[3] Military Medical Academy, Clinic for pulmonology, Belgrade, Serbia
[4] Clinic for lung diseases, Clinical center of Serbia, Belgrade, Serbia, University of Belgrade, Serbia

Uvod: Iako je pleuralni izliv uobičajena klinička manifestacija, diferencijalna dijagnostika uzroka ovog izliva je često izazovna, posebno u ranoj diferencijaciji tuberkuloznog pleuritisa od drugog pleuralnog izliva.

Prikaz slučaja: Predstavljamo ranije zdravog muškarca koji nije imao kontakta sa tuberkuloznom infekcijom, ali je razvio masivni tuberkulozni pleuralni izliv koji je na kraju bio neočekivano tuberkulozan. Počeo je sa tera-

pijom po protokolu i osećao se dobro. Svrha ovog slučaja i pregled literature je bila da se lekari podsete da tuberkuloza nije bolest u nestajanju, već naprotiv – da je u ekspanziji.

Diskusija: Kada pacijent ima novi pleuralni izliv, treba razmotriti dijagnozu tuberkuloznog pleuritisa. Pacijent je pod velikim rizikom za razvoj pulmonalne ili ekstra pulmonalne tuberkuloze ukoliko se dijagnoza ne postavi pravilno. Između 3 i 25% pacijenata sa tuberkulozom će imati tuberkulozni pleuritis, a ovaj procenat je veći kod pacijenata sa oslabljenim imunitetom. Lećenje tuberkuloznog pleuritisa je isto kao i za plućnu tuberkulozu.

Zaključak: Zlatni standard za dijagnostikovanje tuberkuloznog pleuralnog izliva ostaje u detekciji Mycobacterium tuberculosis u pleuralnoj tečnosti, ili uzorcima pleurelne biopsije, bilo mikroskopijom ili kulturom, kao i histološkom verifikacijom kazeoznog granuloma u pleuru zajedno sa kiselim bacilima.

Ključne reči: izliv, pleuritski bol, upala pluća, pleuralna biopsija, tuberkuloza, lečenje.

REFERENCES

1. Global tuberculosis report 2015. Geneva: World Health Organization, 2015.

2. Baumann MH, Nolan R, Petrini M, Lee YC, Light RW, Schneider E. Pleural tuberculosis in the United States: incidence and drug resistance. Chest 2007; 131(4): 1125-32.

3. Light RW. Update on tuberculous pleural effusion. Respirology. 2010; 15(3): 451-8.

4. Light RW. Pleural diseases. 6th edition. Philadelphia: Lippincott Williams & Wilkins; 2013.

5. Chadha SL, Bhagi RP. Treatment outcome in tuberculosis patients placed under directly observed treatment short course (dots) -a cohort study. Ind J Tub. 2000; 47(3): 155-8.

6. Udwadia ZF, Sen T. Pleural tuberculosis: An update. Curr Opin Pulm Med. 2010; 16(4): 399-406.

7. Dutt AK, Moers D, Stead WW. Tuberculous pleural effusion: 6-month therapy with isoniazid and rifampin. Am Rev Respir Dis. 1992; 145(6): 1429–32.

8. Valdes L, Alvarez D, San Jose E, Penela P, Valle JM, García-Pazos JM et al. Tuberculous pleurisy: a study of 254 patients. Arch Intern Med. 1998; 158(18): 2017–21.

9. Seiscento M, Vargas FS, Bombarda S, Sales RK, Terra RM, Uezumi K et al. Pulmonary involvement in pleural tuberculosis: How often does it mean disease activity? Respir Med. 2011; 105(7): 1079–83.

10. Porcel JM, Vives M. Etiology and pleural fluid characteristics of large and massive pleural effusions. Chest. 2003; 124(3): 978–83.

11. Qiu L, Teeter LD, Liu Z, Ma X, Musser JM, Graviss EA.. Diagnostic associations between pleural and pulmonary tuberculosis. J Infect. 2006; 53(6): 377–86.

12. Ong A, Creasman J, Hopewell PC, Gonzalez LC, Wong M, Jasmer RM et al. A molecular epidemiological assessment of extrapulmonary tuberculosis in San Francisco. Clin Infect Dis. 2004; 38(1): 25–31.

13. Torgersen J, Dorman SE, Baruch N, Hooper N, Cronin W.. Molecular epidemiology of pleural and other extrapulmonary tuberculosis: a Maryland state review. Clin Infect Dis. 2006; 42(10): 1375–82.

14. Aljohaney A, Amjadi K, Alvarez GG. A systematic review of the epidemiology, immunopathogenesis, diagnosis, and treatment of Pleural TB in HIV infected patients. Clin Dev Immunol. 2012: 842045.

15. Saks AM, Posner R. Tuberculosis in HIV positive patients in South Africa: a comparative radiological stud with HIV negative patients. ClinRadiol. 1992; 46(6): 387–90.

16. Institut za javno zdravlje, BATUT. Izveštaj o zaraznim bolestima u Republici Srbiji, 2018.god.Available on: www. batut.org.rs/ download /izvestaji/ Godisnji%20 izvestaj%20 zarazne%20bolesti%202017.pdf.

17. Porcel JM. Tuberculous pleural effusion. Lung. 2009; 187(5): 263–70.

18. Payam N, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/ Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. 2016; 63: 853-67.

19. Schunemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. Am J RespirCrit Care Med. 2006; 174(5): 605–14.

20. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008; 336(7650): 924–6.

Correspondence to/Autor za korespondenciju
Biljana Lazović
University Clinical Center „Zemun“, Belgrade, Serbia
Vukova 9, Zemun, 11080 Belgrade
Self phone +381 62212040
Fax +381 2141569
lazovic.biljana@gmail.com

SANAMED
2019; 14(2): 199–202
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i2.339
UDK: 616.36-073
ID: 278330892
Case report

ACCESORY AND ECTOPIC LIVER LOBE AT SAME PATIENT: CASE REPORT

Vasin Dragan,[1] Doklestić Krstina,[2] Stojadinović Milica,[1] Filipović Aleksandar,[1] Kovač Jelena,[1] Mašulović Dragan[1]

[1] Center for radiology and MRI, Clinical center of Serbia, Belgrade, Serbia
[2] Clinic for emergency surgery, Clinical center of Serbia, Belgrade, Serbia

Primljen/Received 27. 05. 2019. god.

Prihvaćen/Accepted 20. 07. 2019. god.

Abstract: **Introduction:** Accessory liver lobes (ALL) are defined as supranumerary liver lobes, composed of normal liver parenchyma in continuity with the liver, in contrast to ectopic liver lobes (ELL) that have no anatomical continuity with the normal liver. **Case report:** In this article we report on a rare radiological diagnosis of an synchronous accessory and ectopic liver lobe using ultrasonography (US) and computed tomography (CT). A 59-year-old female with no symptoms was admitted to our hospital due to preventive exam. Abdominal ultrasonography revealed a high echoic 6 cm x 5 cm soft tissue area in right anterior subhepatic space with distinct margins, a uniform echo and blood flow and was suspected to be abdominal tumor. An enhanced abdominal computed tomography (CT) showed the irregular 65 mm x 48 mm x 32 mm mass in the right hypochondrium below IV and V liver segment with clear margins, a uniform density, texture and contrast enhancement as normal liver tissue. In same patient CT also showed small 16 mm x 12 mm mass in posterior mediastinum in right retrocrural space so diagnosis of accessory and ectopic liver lobe was confirmed. An accessory liver lobe is adjacent and attached to the liver by its own mesentery, while an ectopic liver lobe is one that is completely detached from the normal liver parenchyma. **Conclusion:** Ultrasound can show mass in the abdomen, which is most commonly in the subhepatic area, but very rarely can initially diagnose ALL or ELL due to different echogenicity of the liver parenchyma in different acoustic windows. In the case of an atypical CT presentation, an MR examination of the abdomen is indicated but it is very rarely. Fast and accurate radiological diagnosis of ALL and ELL is important in the prevention of unnecessary invasive diagnostic procedures such as laparotomy and thoracotomy which are needed only in cases of complications.

Key words: ultrasound, CT, accesory, ectopic, liver.

INTRODUCTION

Accessory liver lobes (ALL) are defined as supernumerary liverlobes, composed of normal liver parenchyma in continuity with the liver, in contrast to ectopic liver lobes (ELL) without anatomical continuity with the normal liver (1). ALL and ELL were considered as a rare development anomaly. Most cases with an ALL are asymptomatic, and usually accidentally find on cross-sectional imaging, laparotomy or autopsy (2). Although, in rare cases, it can cause abdominal pain and liver dysfunction. It is presented a rare radiological case of synchronous accessory and ectopic liver lobe, using ultrasonography (US) and computed tomography (CT).

CASE PRESENTATION

A 59-year-old female with no symptoms was admitted to our hospital for routine exam. She had no relevant past medical or surgical history. The abdomen was soft, with no palpable masses. Abdominal ultrasonography revealed a high echoic 6 cm x 5 cm soft tissue area in right anterior subhepatic space, with distinct margins, and uniform echo and blood flow. It was suspicious of the presence of abdominal tumor (Figure 1a-b). The laboratory data showed normal hepatic function, with anaspartate transaminase (AST) level of 21 U/L (0–40), alanine transaminase (ALT) level of 26 U/L (0–41), gamma-glutamyl transferase (GGT) level of 20 U/L (0-30) and bilirubin level 0.5 mg/dl (0.2-1mg/dl).

An enhanced abdominal computed tomography (CT) showed irregular 65 mm x 48 mm x 32 mm mass in the right hypochondrium, below segments IV and V of the liver, with clear margins and uniform density,

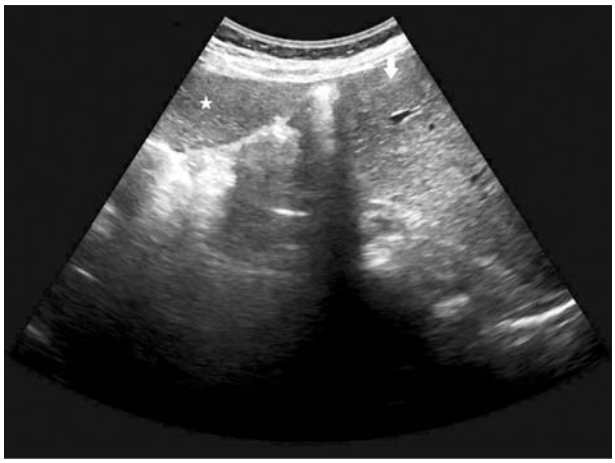


Figure 1a. *Abdominal ultrasonography – sagital scan: high echoic soft tissue area (star) in subhepatic space with distinct margins and uniform echo with suspected connection to the right liver lobe (arrow)*

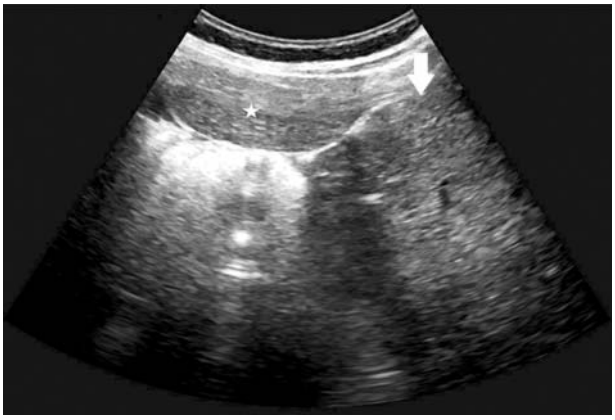


Figure 1b. *Abdominal ultrasonography – oblique scan: soft tissue area (star) in subhepatic space with suspected connection to the right liver lobe (arrow)*

texture and contrast enhancement as normal liver tissue (Figure 2a-b). Mass was attached to the caudal part of segment V of the liver by a thin stalk of liver tissue, that contained a vascular pedicle. After CT exam abdominal ultrasonography was performed again, and color-doppler signal of the hepatic vein (Figure 3) was seen at the level of the stalk. These findings suggest the diagnosis of ALL. CT also showed small 16 mm x 12 mm mass in the right retrocrural space of posterior mediastinum (Figure 4a-b), with the same CT features as liver tissue but without tissue or vascular connection to the liver. That helped to confirm diagnosis of ELL.

DISCUSSION

An accessory liver lobe is a rare congenital development anomaly that is usually asymptomatic and mostly detected accidentally at laparotomy (4). It occurs from an error in the development of the endodermal caudal foregut, during the third gestational week,

Figure 2a. *Contrast enhanced abdominal CT – multiplanar coronal reconstruction: solid mass (star) in the right hypochondrium below IV and V liver segment with clear margins, a uniform density, texture and contrast enhancement as normal liver tissue, attached to the caudal pole of liver segment V by a thin stalk of liver tissue that contained a vascular pedicle (arrow) – CT feature of accessory liver lobe*

Figure 2b. *Contrast enhanced abdominal CT – sagital reconstruction: solid mass (star) in the right hypochondrium below IV and V liver segment attached to the caudal pole of liver segment V by a thin stalk of liver tissue that contained a vascular pedicle (arrow)*

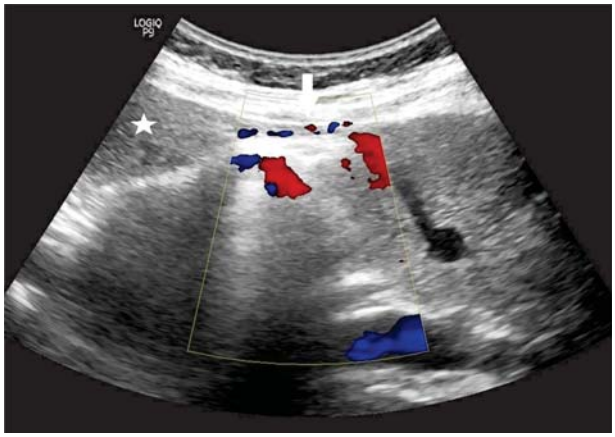


Figure 3. *Abdominal color-doppler ultrasonography – sagital scan: soft tissue area (star) in subhepatic space with vascular connection (star) to the right liver lobe*

Figure 4a. *Contrast enhanced abdominal CT – axial scan: small mass (arrow) in posterior mediastinum in right retrocrural space, same CT characteristics as liver tissue but without tissue or vascular connection to the liver – CT feature of ectopic liver lobe*

and segmentation of the hepatic bud (5). An accessory liver lobe is adjacent and attached to the liver by its own mesentery, while an ectopic liver lobe is one that is completely detached from the normal liver parenchyma (6). Four types of accessory liver has been described in the literature: big accessory hepatic lobe (> 30 g), small accessory hepatic lobe (< 30 g), ectopic lobe with no liver connection, and microscopic accessory lobe in the gallbladder wall (3).

The development of new imaging methods such as US, CT and MR detect an increasing number of ALLs during examination performed for unrelated cause.

Ultrasonography is the mostly used initial imaging method in the abdominal pathology. Ultrasound can show mass in the abdomen, which is most commonly located in the subhepatic space, but rarely can initially confirm ALL or ELL, due to different echogenicity of

Figure 4b. *Contrast enhanced abdominal CT – multiplanar coronal reconstruction: small mass in right retrocrural space, same CT characteristics as liver tissue but without tissue or vascular connection to the liver – CT feature of ectopic liver lobe*

the liver parenchyma in different acoustic windows. In some cases, the color doppler scan can be useful in detection a blood supply within the liver parenchyma, but it can not exclude pedunculated liver tumors. Therefore, the ultrasound examination could raise suspicion of the presence of abdominal tumor, but CT scan is necessary as a next diagnostic step, to confirm diagnosis.

CT findings of ALL are following: (i) significant part of the accessory lobe has the same density or signal as normal liver tissue; (ii) the ALL have distinct and smooth margins, with complete demarcation; (iii) the ALL is connected with normal liver tissue over a stalk of tissue or base; (iv) vein presentation in ALL was apparent during enhanced CT scanning (7). In the rare case of atypical CT presentation, abdominal MR image is indicated. Ectopic ALL within the thorax may be misdiagnosed for pulmonary, pleural or diaphragmatic tumor, depending on its location (8).

Asymptomatic patients with ALL and ELL accidentally discovered, do not require any treatment. Complications related to ALL includes torsion, infarction, hemorrhage and fracture of the accessory lobe, and may require urgent laparotomy (2).

CONCLUSION

Prompt and accurate radiological diagnosis of ALL and ELL is important in the prevention of unnecessary invasive diagnostic procedures such as laparotomy or thoracotomy, which are needed only in cases of complications.

Abbreviations

MR — magnetic resonance
ALL — Accessory liver lobes

ELL — ectopic liver lobes
US — ultrasonography
CT — computed tomography

Acknowledgment: None

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Sažetak

AKCESORNI I EKTOPIČNI LOBUS JETRE KOD ISTOG PACIJENTA: PRIKAZ SLUČAJA

Vasin Dragan,[1] Doklestić Krstina,[2] Stojadinović Milica,[1] Filipović Aleksandar,[1] Kovač Jelena,[1] Mašulović Dragan[1]

[1] Center for radiology and MRI, Clinical center of Serbia, Belgrade, Serbia
[2] Clinic for emergency surgery, Clinical center of Serbia, Belgrade, Serbia

Uvod: Akcesorni lobusi jetre (ALL) se definišu kao prekobrojni lobusi jetre, koji su sastavljeni od normalnog parenhima jetre, u odnosu na ektopične lobuse jetre (ELL), koji nemaju anatomski kontinuitet sa normalnom jetrom. **Prikaz slučaja:** U ovom radu je prikazan slučaj retke radiološke dijagnoze sinhronog postojanja akcesornog i ektopičnog jetrinog lobusa koristeći ultrazvuk (UZ) i kompjuterizovanu tomografiju (CT). 59-godišnja pacijentkinja bez simptoma je bila primljena u našu bolnicu, radi preventivnog pregleda. Ultrazvukom abdomena otkriveno je izraženo ehogeno polje mekog tkiva 6 x 5 cm u desnom prednjem subhepatičnom prostoru sa jasnim marginama. S obzirom na postojanje kolor-dopler signala postavljena je sumnja na tumorsku promenu u abdomenu. Kompjuterizovana tomografija (CT) nakon intravenske aplikacije kontrasta je pokazala mekotkivnu promenu dijametara 65 mm x 48 mm x 32 mm u desnom hipohondrijumu ispod IV i V segmenta jetre, oštrih kontura, uniformnih denziteta, teksture i kontrastne opacifikacije koja bi odgovarala normalnom tkivu jetre. Kod istog pacijenta CT je pokazao malo polje 16 mm x 12 mm u posteriornom medijastinumu u desnom retrokruralnom prostoru. S toga je dijagnoza akcesornog i ektopičnog jetrinog lobusa bila potvrđena. **Zaključak:** Akcesorni režanj jetre se najčešće javlja u subhepatičnom prostoru ali se retko inicijalno dijagnostikuje iz razloga različite ehogenosti od parenhima jetre koja je posledica različitih akustičnih prozora. Brza i precizna radiološka dijagnoza ALL i ELL je važna u prevenciji nepotrebnih invazivnih dijagnostičkih procedura, kao što su laparotomija i torakotomija, koje su potrebne samo u komplikoovanim slučajevima.

Ključne reči: ultrazvuk, CT, akcesorni deo, ektopičnost, jetra.

REFERENCES

1. Morris Jr MW, Helling TS, Creswell LL, Jordan B, Mitchell EM. Ectopic liver masquerading as a floating intracaval mass. J Vasc Surg. 2012; 55(6): 1759–61.

2. Kapoor A, Harshavardhan KR, Mutnuru PC, Narayanan R. Accesory hepatic lobe – A „not so rare“ entity. Int. J. Anat, Surg and Radiol. 2017; 6(2): 26-30.

3. M. Massaro, M. P. Valencia, M. Guzman, Mejja J. Accessory hepatic lobe mimicking an intra-abdominal tumor. J. Comput. Assist. Tomogr. 2007; 31 (4): 572–3.

4. Ladurner R, Brandacher G, Mark W, Iannetti C, Lottersberger C, Steurer W, et al. Complete hepatic ischemia due to torsion of a large accessory liver lobe: first case to require transplantation. Transpl Int. 2005; 18(4): 467-9.

5. Carrabetta S, Piombo A, PodestB R, Auriati L. Torsion and infarction of accessory liver lobe in young man. Surgery. 2009; 145(4): 448-9.

6. Jambhekar K, Pandey K, Kaushik P, Shah HP. Intermittent torsion of accessory hepatic lobe: An unusual cause of recurrent right upper quadrant pain. Indian J Radiol Imaging. 2010; 20(2): 135-7.

7. Wang C, Cheng L, Zhang Z, Xie T, Ding H, Deng Q et al. Accessory lobes of the liver: A report of 3 cases and review of the literature. Intractable Rare Dis Res. 2012; 1(2): 86-91.

8. Wang Y, Junlin L, Zhang WG, Chen JH, He Y, Chen JM. Accessory lobe of right liver mimicking a pulmonary tumor in an adult male. Ann Thorac Surg. 2010; 89(2): e9-10.

Correspondence to/Autor za korespondenciju
Dragan Vasin, MD
Center for radiology and MRI, Clinical center of Serbia
Street Vojvode Micka 1i, Belgrade, Serbia
email: draganvasin@gmail.com

SANAMED
2019; 14(2): 203–208
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i2.327
UDK: 616.61-022.1:612.662-055.2
ID: 278332172
Review article

INFECTION OF URINARY TRACT IN MENOPAUSAL WOMEN

Smieško Gordana[1, 2]

[1] Institute of Public Health of Vojvodina,Novi Sad, Serbia
[2] Department of Microbiology, Faculty of Medicine Novi Sad, University of Novi Sad, Serbia

Primljen/Received 07. 03. 2019. god. Prihvaćen/Accepted 16. 04. 2019. god.

Abstract: Urinary infections are, by frequency, in the second place, immediately behind respiratory infections. The prevalence of urinary tract infections is generally increasing. UTI (urinary tract infections) is more common in women and very young people. The rates of occurrence generally reflect predisposing factors such as congenital anomalies in childhood, the onset of sexual activity, especially in women, and, of course, postmenopausal changes in older women. It is assumed that 50-60% of women can expect an episode of urinary infection during their lifetime. In postmenopausal women, there is a deficit in estrogen. It is one of the important factors that indirectly protects the vaginal mucous membranes as well as the uroepitel from infection. Bacteria from the digestive tract colonize the skin of the perineum, then the vulva, the vagina and the outer opening of the urethra. Normal vaginal flora (lactobacilli) protects the vagina from colonization by fecal bacteria because it lowers pH and creates unfavorable conditions for survival of bacteria.

Key words: urinary tract, infections, menopausal, women.

INTRODUCTION

Urinary infections are, by frequency, in the second place, immediately behind respiratory infections. The prevalence of urinary tract infections is generally increasing. UTI (urinary tract infections) is more common in women and very young people. The rates of occurrence generally reflect predisposing factors such as congenital anomalies in childhood, the onset of sexual activity, especially in women, and, of course, postmenopausal changes in older women. It is assumed that 50-60% of women can expect an episode of urinary infection during their lifetime. Studies confirm that annually, consulting a general practitioner for urinary infection, requires 14 men and 60 women out of 1,000 examined. If E. coli is previously isolated, the risk of the infection recurring over the next 6 months is 23.7%, unlike other causes, when the infection returns to 7.7% of cases (1). It is estimated that around 150 million cases worldwide have an annual incidence of this type of infection, with more than 5.3 million euros being spent for direct care. The most common causes of urinary infections are bacteria, but other microorganisms such as fungi, parasites and protozoa can cause the development of urinary infections. Although Escherichia coli is the most common cause of urinary infections, only some of its strains have the ability to adhere to the mucous membrane and challenge the change. She is Gram-negative, optional anaerobic, movable bacilli. They are arranged individually, in pairs or in irregular groups. They have chains or fimbres that have an adhesive role. They have complex antigen material. The most important are O antigen that is thermostable and H antigen that is thermolabile. Fimbria antigens have appropriate adhesive properties. Additional surface virulence factors are flagels that allow mobility and easier access to the target tissue (1, 2, 3).

PATHOGENESIS

Urinary infection occurs when the bacteria enter the urine and overpower the defenses of uroepithel by their virulence. Urine is under normal circumstances sterile, i.e. It does not contain bacteria or other microorganisms. Most urinary infections are caused by bacteria that make up the normal flora of the gut (Escherichia coli, Enterobacter, Klebsiella, Proteus spp.) These bacteria are normal inhabitants of the bowel, but if they find themselves in the urinary tract they cause an infection. Because of the close proximity of the anus and urethral opening, the urethra is often contaminated through the perineum and urethritis is formed. Given that infection usually develops accidently, inflammation spreads to the urinary bladder, causing cystitis. If the etiological factor is very virulent or there are signif-

icant host risk factors, then the infection can easily spread to the kidneys in which pyelonephritis occurs. If the human defenses are very weak and the therapy is not introduced timely, microorganisms enter the blood with the resulting bacteremia and sepsis, which can end up fatal. Ascendant spread of the infection is particularly characteristic for strains with specific adhesins, i.e. P-fimbriums adhering to the urotel (4, 5, 6, 7).

In postmenopausal women, there is a deficit in estrogen. It is one of the important factors that indirectly protects the vaginal mucous membranes as well as the uroepitel from infection. Bacteria from the digestive tract colonize the skin of the perineum, then the vulva, the vagina and the outer opening of the urethra. Normal vaginal flora (lactobacilli) protects the vagina from colonization by fecal bacteria because it lowers pH and creates unfavorable conditions for survival of bacteria. However, the disruption of this flora (the use of some spermicides and broad spectrum antibiotics, post-menopausal estrogen deficiency, irregular hygiene) makes it easier to colonize the vagina with uropathogenic bacterial strains, their settlement in the urethra and the onset of IUT (8, 9, 10, 11). Incontinence of the urine and, consequently, constant moistening of the periphery region allows easier duplication of bacteria and facilitates penetration into the urethra and the occurrence of inflammation. In addition to menopause, which leads to decreased uropeal defenses, and diabetes can lead to microalbuminuria with later impaired glomerular filtration and more difficult to wash bacteria that are left in the urinary tract and easily lead to infection (12, 13). There is also the possibility of spreading infection from distant hematogenic or lymphatic pathways, although this is a much less common way of urinary infections (14, 15, 16).

CLINICAL PICTURE

Urinary infections in the general population, as well as in women in postmenopausal, can affect only certain parts of the urinary system or extend to the entire urinary tract and beyond.

Asymptomatic bacteriuria

It implies colonization of the urinary tract with bacteria, not a classic infection. There is significant bacteriuria, but it does not cause any problems. The frequency of asymptomatic bacteriuria increases with age, and especially in men and women after 65 years. The significance of asymptomatic bacteriuria and the indication for treatment varies depending on whether it is detected in patients with normal urinary system or in those who have any complicated disease or condition. In non-risk categories, therapy is not required because of the potential for antibiotic resistance to bacteria. Many studies have indicated that most women with asymptomatic bacteriuria who are not pregnant and who do not have complicated urinary tract disorders after a while spontaneously eliminate bacteria (17, 18, 19).

Cystitis

Acute uncomplicated cystitis is the most common form of urinary infection. It is characteristic for women in the sexually active period and for women in menopause. Symptoms generally develop rapidly, within hours or during the day. Begin with more frequent urination, baking in urination, pain in the bladder at the end and immediately after wetting. The patient very often wets a few drops of urine, has the impression that her bladder has not been emptied, false urine calls (tinges), accompanied by strong pain and feeling of pressure in the bladder area, occur. Terminal or total haematuria may occur. The general condition at the beginning is not disturbed, but if timely treatment is not started, anger, fever, and elevated temperatures can occur, which is already in favor of pyelonephritis.

Women in menopause are characterized by recurrent cystitis, 10-15% of women suffer from this type of disease. These women appear because of the weakened urotract defense defenses, and this is a re-entry of bacteria into the urinary tract, and not about the ill-treated previous acute cystitis (20, 21, 22).

Pyelonephritis

Pyelonephritis is a bacterial infection of the renal pelvis and kidney parenchyma. The most common inflammation extends ascendant from the urinary bladder, although possible haematogenous and lymphopenia pathways of expansion with the consequent renal inflammation. The clinical picture develops rapidly and is characterized by high temperature (up to 40 °C), anger, fever, lumbar pain and digestive symptoms (nausea and vomiting). Concurrent cystitis is present in one third of patients.

There is painful sensitivity of the lumbar lodge to succulent. Very often both kidneys are affected. The progression of uncomplicated bacterial cystitis into acute uncomplicated pyelonephritis is expected in only 2% of patients, regardless of whether they are treated or not (23).

COMPLICATIONS

Urosepsa

Urosepsa is a septic condition caused by the penetration of bacteria and bacterial toxins from the urinary tract into the bloodstream. It is reported in people with

urological manipulations, where bacteria are of extreme virulence, as well as in people with impaired immunity and associated illness. Menopausal women are especially affected due to extremely common urinary infections, some of which may lead to septic conditions. Especially dangerous is sepsis caused by pseudomonas due to the high mortality rate. Clinically, the temperature (over 38 °C) with fever or hypothermia (below 36 °C), leukocytosis (over 12,000), tachycardia and tachypnoea and disturbances of consciousness (24).

Abscess of the kidney

It represents a localized pulmonary collection that can be formed in the cortex (cortical abscess) or kidney medulla (medullary abscesses). Medullary abscesses mainly develop on the basis of the already existing urinary tract infection (acute pyelonephritis), while cortical abscesses are more often metastasized from a distant inflammatory site. The kidney abscess is expressed by signs of acute infection (high temperature, fever, fever) with pain in the affected area of the kidneys. Symptoms of lower urinary tract infection may not be present.

Perinefritic abscess

Perinefritic abscess is the acute inflammation of the tissue around the kidneys. It is most often the result of the penetration of bacteria from the inflammatory site of the kidney. The inflammatory process takes place in the loose connective tissue and fat tissue around the kidneys (25). Clinically manifests itself with febrile, painful sensation and redness of the skin in the lumbar region.

DIAGNOSIS

The diagnosis of urinary infections is based on the anamnesis and clinical picture and is confirmed by additional analyzes. In addition to the clinical picture, biochemical analysis of urine and urinary culture is often used to prove the existence of an infection. The interpretation of the findings should be careful, because there is always a possibility of contamination of the sample, regardless of the method it was obtained. The most common method of taking a sample is to collect the medium jet of the first morning urine into the sterile container after allowing the first jet to drain in order to reduce the possibility of contamination.

The presence of bacteria in urine (bacteriuria) can, but does not necessarily mean, an infection. In order to delineate whether their presence signifies an infection or is a consequence of contamination, a concept of significant bacteriuria has been introduced, which indicates the presence of more than 100,000 bacteria in 1ml of urine, which most often represents infection rather than contamination.

Nitrites in the urine are highly specific for the presence of bacteria, but their absence does not necessarily mean the absence of infection, but can be the result of dilution of urine due to the introduction of a large amount of fluid or the use of diuretics. In addition, some bacteria that cause IUTs do not lead to the reduction of nitrates to nitrites (Staphylococcus, Enterococcus, and Pseudomonas). Nitrites can also be positive for green-eating nutrition. Diagnosis of acute uncomplicated cystitis with a high probability (> 90%) can be set only on the basis of a clinical picture (provided three or more typical symptoms are present at the same time). Urinoculture is a gold standard to prove infection, not only for determining the presence of a pathogen, but also for the ability to know what type of microorganism is and what its sensitivity to antimicrobial therapy is. However, there are limits to the diagnosis of infections in which the number of bacteria is less than 100 000 in ml of urine (in case of infections of the lower part of the UT). As many laboratories as the reference value for the detection of infection take a number of 100,000 or 10,000 bacteria per ml, negative urinary effects of the urinary crops should be interpreted with caution. In most cases, urine examination shows massive leukocytosis and bacteriuria. Proteinuria may also be present, as is the finding of leukocytic cylinders that, with massive leukocytes, provide reliable evidence of pyelonephritis. Of the other laboratory analyzes, complete blood count (CKS), C-reactive protein (CRP), serum creatinine and serum creatinine should be made. Radiological methods should be considered if it is necessary to exclude the existence of obstruction or calculus UTI.

THERAPY

The main therapy for urinary infections are antibiotics.

The treatment of acute uncomplicated cystitis and uncomplicated pyelonephritis in women in menopause is empirically. When selecting an adequate antimicrobial drug, care should be taken of the type of causative agent and its susceptibility to the drug, price and availability, as well as the possibility of allergic and other adverse reactions.

Trimethoprim-sulfamethoxazole (TMP-SMK) showed a high rate of eradication of uropathogens and many put it into the first-line treatment for the treatment of acute uncomplicated cystitis in menopausal women. Three-day TMP-SMK therapy leads to eradication of the causative factor in 93% of women. The

same studies showed the same three-day efficacy compared to seven-day therapy and significantly less frequent adverse reactions. In pyelonephritis, it is not enough that the medicine reaches a high concentration in the urine, but it must be sufficient in the blood to renal tissue. This drug is not the first choice in pyelonephritis, but is applied only after antibiography and proven sensitivity of the causative agent to it. What complicates the use of TMP-SMK is the emergence of an increasing number of resistant strains of E. coli on this drug. Alternatively, a single dose can be used with nitrofurantoin or phosphomycin-trometamol therapy. Both of these the drug has a low resistance rate, and only 5-10% have lower efficacy compared to the three-day TMP-SMK therapy in eradicating the cause and improving clinical symptoms. Nitrofurantoin should be used with caution in elderly women in menopause with comorbidities due to the potential for toxic effects that are most pronounced on the lungs and liver after long-term use.

Fluoroquinolones (ofloxacin, ciprofloxacin, levofloxacin) in many studies have shown the same efficacy as TMP-SMK. It is recommended that quinolones be used as drugs of the second choice in the treatment of uncomplicated cystitis, although in practice this is not observed. In the case of pyelonephritis, ciprofloxacin is a first-line medication. Initially, 1 g of ceftriaxone or aminoglycoside (24h-dose) may be administered parenterally in pyelonephritis and then continued with ciprofloxacin per so. Currently, in Europe and North America, resistance is less than 10%, but there is a trend of increasing resistance that is becoming worrying. In over 90% of cases, cystitis causes complete withdrawal of symptoms. If the symptoms are delayed even after the use of antibiotics, it is necessary to do urinology. If the symptoms are very pronounced then another antibiotic should be introduced immediately obtaining the antibiogram results (25).

If it is a severe clinical picture of acute uncomplicated pyelonephritis where systemic signs of infection (nausea, vomiting) are present, haemodynamic instability or signs of sepsis as well as in the suspected complication of the infection, it is necessary to hospitalize the patient. Complicated IUT is much more difficult to cure. The spectrum of possible causes is much higher. In addition, they are often resistant and sometimes multiresistant to antibiotics that are used. Therapy begins with empirical broad spectrum antibiotics (cephalosporin's III generation, fluorinated quinolones) and continues with targeted antibiogram therapy. Treatment of complicated IUT implies the simultaneous removal of factors that make them complicated. In recurrent IUT, if the infection recurs within one month of completion of the primary inflammation treatment, an antibiotic of the first therapeutic line should be included in the short-term regimen. In the event that the infection occurs within 6 months, it is necessary to choose another antibacterial drug, especially if the first choice was TMP-SMK. In other cases, recurrent infection should be treated by the same therapeutic protocol as sporadic cases of uncomplicated urinary infections. Treatment is always started empirically and, if necessary, corrected after getting antibiotics.

PREVENTION

Prevention of IUT in menopausal women is of utmost importance in the sound of high incidence of infection. Prior to the initiation of antimicrobial prophylaxis, non-medicaments prevention measures should be carried out. This implies a lifestyle change in order to reduce risk factors, but also other measures that have shown efficacy in the prevention of recurrent IUTs (cranberry consumption and vaginal use of estrogen). Changing the lifestyle of women in menopause involves, first and foremost:

Reduction of foods and beverages that irritate the bladder, especially caffeine preparations

• More often than not a little exercise to bubble bacteria (at 2-3 hours)

• Kegel exercises for muscle strengthening give pelvis and incontinence prevention

• Cessation of smoking - chronic cough stimulates urinary bladder urinary tract and easier penetration of bacteria

• Maintenance of normal body weight-elevated BMI stimulates incontinence

• After urinating, sweeping the perineum from front to back

• Consuming as much fluid as possible due to easier washing of bacteria from UT

• Avoiding hard and synthetic underwear.

CONCLUSION

Urinary infections are one of the most common infections in humans. According to the frequency they are located immediately behind the respiratory. Women at menopause are at particular risk due to decreased estrogen concentrations, which is a very important factor in the defense against urogenital infections. In women who have severe recurrent infection with vaginal disorders (dyspareunia, dryness), mandatory substitution therapy is required for local estrogens using topical tablets, creams or rats with gradual release of estrogens placed in the vagina. Per orally estrogen-containing estrogen does not have a sufficiently pronounced local effect that will reduce the incidence

of IUT and have more pronounced adverse effects. In addition to estrogen, personal hygiene, changes in lifestyle habits, use of cranberry preparations and, if necessary, long-term use of small doses of antibiotics, which in more than 95% of cases manage to completely prevent the development of IUT, is very important.

DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

Source of support: None

Acknowledgement

This research did not receive any specific grant from funding agencies or non-profit sectors.

Licensing

Sažetak

INFEKCIJE URINARNOG TRAKTA KOD ŽENA U MENOPAUZI

Smieško Gordana[1, 2]

[1] Institute of Public Health of Vojvodina,Novi Sad, Serbia
[2] Department of Microbiology, Faculty of Medicine Novi Sad, University of Novi Sad, Serbia

Urinarne infekcije su, prema učestalosti, na drugom mestu, odmah iza respiratornih. Prevalenca infekcije urinarnog sistema je generalno u porastu. UTI (infekcije urinarnog trakta) je češća kod žena i veoma mladih osoba. Stope pojave generalno reflektuju predisponirajuće faktore kao što su kongenitalne anomalije u detinjstvu, započinjanje seksualne aktivnosti, naročito kod žena, i naravno, postmenopauzalne promene kod starijih žena. Pretpostavlja se da 50-60% žena može očekivati epizodu urinarne infekcije u toku svog života. Kod žena u postmenopauzi dolazi do deficita u količini estrogena. On je jedan od važnih faktora koji indirektno štite vaginalnu sluznicu kao i uroepitel od infekcije. Bakterije iz digestivnog trakta kolonizuju kožu perineuma, zatim vulvu, vaginu i spoljni otvor uretre. Normalna vaginalna flora (laktobacili) štiti vaginu od kolonizacije fekalnim bakterijama jer snižava pH vrednost i stvara nepovoljne uslove za preživljavanje bakterija.

Ključne reči: urinarni trakt, infekcije, menopauza, žene.

REFERENCES

1. Foxman B, Brown P. Epidemiology of urinary tract infections: transmission and risk factors, incidence, and costs. Infect Dis Clin North Am. 2003; 17(2): 227–41.

2. Wagenlehner FME, Hoyme U, Kaase M,Fünfstück R, Naber KG, Schmiemann G. Clinical practice guideline: uncomplicated urinary tract nfections. Dtsch Arztebl Int. 2011; 108(24): 415-23.

3. Ronald A. The etiology of urinary tract infection:traditional and emerging pathogens. Am J Med. 2002; 113(suppl 1A): 14S–19S.

4. Epp A, Larochelle A, Lovatsis D, Walter JE, Easton W, Farrell SA et al. Recurrent Urinary Tract Infection. J Obstet Gynaecol Can. 2010; 32(11): 1082-90.

5. Kodner CM, Gupton EKT. Recurrent urinary tract infections in women: dyagnosis and management. Am Fam Physician. 2010; 82(6): 638-43.

6. Aso T, Uchiyama S, Matsumura Y, Taguchi M, Nozaki M, Takamatsu K, et al. A natural S-equol supplement alleviates hot flushes and other menopausal symptoms in equol nonproducing postmenopausal Japanese women. Journal of Women's Health. 2012; 21(1): 92–100.

7. Benrubi GI. Hand book of obstetric and gynecologic emergencies (Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins, 2010.

8. Cibulka Nj, Barron ML. Guidelines for nurse practitioners in ambulatory obstetric settings, New York, Springer Publishing Company, 2013.

9. Hooton TM. Uncomplicated urinary tract infection. N Engl J Med 2012; 366(11): 1028-37.

10. Stamm WE, Norrby SR. Urinary tract infections: disease panorama and challenges. J Infect Dis. 2001; 183(suppl 1): S1-4.

11. Berger-Jekić O, Dinić M, Đukić S, Jelesić Z, Kocić B, Kulauzov M et al. Medicinska bakteriologija. Beograd; Savremena administracija a.d., 2008.

12. Johnsson KM, Ptaszynska A, Schmitz B, Sugg J, Parikh SJ, List JF. Urinary tract infections in patients with diabetes treated with dapagliflozin. J Diabetes Complications. 2013; 27(5): 473-8.

13. Mc Cormick T, Ashe RG, Kearney PM. Urinary tract infection in pregnancy. The Obstetrician and Gynaecologist. 2008; 10(3): 156-62.

14. Soto MS. Importance of biofilms in urinary tract infections: new therapeutic approaches. Advances in Biology. 2014; 13.

15. Ramakrishnan K, Scheid DC. Diagnosis and management of acute pyelonephritis in adults. Am Fam Physician. 2005; 71(5): 933-42.

16. Pallett A, Hand K. Complicated urinary tract infections: practical solutions for the treatment of multiresistant Gram-negative bacteria. J Antimicrob Chemother 2010; 65(3): iii25–33.

17. Young JL, Soper DE. Urinalysis and urinary tract infection: update for clinicians. Infect Dis Obstet Gynecol. 2001; 9(4): 249–55.

18. Wilson ML, Gaido L. Laboratory diagnosis of urinary tract infections in adult patients. Clin Infect Dis. 2004; 38(8): 1150–8.

19. Knottnerus BJ, Bindels PJE, Geerlings SE, Moll van Charante EP, Ter Riet G. Optimizing the diagnostic work-up of acute uncomplicated urinarytract infections. BMC Fam Pract 2008; 9:64 doi: 10.1186/1471-2296-9-64

20. Burdi EM, Kehl SK. A critical appraisal of the role of the clinical microbiology laboratory in the diagnosis of urinary tract infections. J Clin Microbiol. 2011; 49(9): S34–8.

21. Grabe M, Bartoletti R, Bjerklund Johansen TE, Cai T, Çek M, Köves B et al. Guidelines on urological infections. European Association of Urology 2015. Available online at:http://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf.

22. Fihn SD. Acute uncomplicated urinary tract infection in women. N Engl J Med. 2003; 349(3): 259-66.

23. Franz M, Hörl WH. Common errors in diagnosis and management of urinary tract infection. I: Pathophysiology and diagnostic techniques. Nephrol Dial Transplant. 1999; 14 (11): 2746-53.

24. Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. Urol Clin N Am. 2008; 35(1): 1–12.

25. Schmiemann G, Kniehl E, Gebhardt K, Matejczyk MM, Hummers-Pradier E. The diagnosis of urinary tract infection: a systematic review. Dtsch Arztebl Int. 2010; 107(21): 361–7.

Correspondence to/Autor za korespondenciju
Gordana Smieško
Department of Microbiology, Faculty of Medicine Novi Sad
University of Novi Sad, Serbia, Institute of Public Health
Futoška 121, 21000 Novi Sad, Serbia
e-mail: gordana.bojic@mf.uns.ac.rs
Phone: +381 (0) 60 5115771

UPUTSTVO AUTORIMA

SANAMED je medicinski časopis osnovan 2006. godine. Časopis objavljuje: originalne naučne i stručne članke, prikaze bolesnika, revijske radove, pisma uredniku, članke iz istorije medicine, prikaz objavljenih knjiga i druge medicinske informacije.

Rukopise slati na adresu:
Prim. dr Avdo Ćeranić,
(za Sanamed)
Ul. Palih boraca 52, 36300 Novi Pazar
Email: sanamednp2006@gmail.com
www.sanamed.rs

Prispeli rukopis Uređivački odbor šalje recenzentima radi stručne procene. Ukoliko recenzenti predlože izmene ili dopune, kopija recenzije se dostavlja autoru s molbom da unese tražene izmene u tekst rada ili da argumentovano obrazloži svoje neslaganje s primedbama recenzenta. Konačnu odluku o prihvatanju rada za štampu donosi glavni i odgovorni urednik.

Časopis se štampa na engleskom jeziku, sa kratkim sadržajem prevedenim na srpski jezik.

OPŠTA UPUTSTVA

Tekst rada kucati u programu za obradu teksta *Word*, latinicom, sa dvostrukim proredom, isključivo fontom *Times New Roman* i veličinom slova 12 tačaka (12 pt). Sve margine podesiti na 25 mm, a tekst kucati sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm, bez deljenja reči (hifenacije).

Rukopis mora biti organizovan na sledeći način: naslovna strana, sažetak na srpskom jeziku, sažetak na engleskom jeziku, ključne reči, uvod, cilj rada, bolesnici i metodi/materijal i metodi, rezultati, diskusija, zaključak, literatura, tabele, legende za slike i slike.

Svaki deo rukopisa (naslovna strana, itd.) mora početi na posebnoj strani. Sve strane moraju biti numerisane po redosledu, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u zagradama, i to onim redosledom kojim se pojavljuju u tekstu.

Obim rukopisa. Celokupni rukopis rada, koji čine naslovna strana, kratak sadržaj, tekst rada, spisak literature, svi prilozi, odnosno potpisi za njih i legenda (tabele, slike, grafikoni, sheme, crteži), naslovna strana i sažetak na engleskom jeziku, mora iznositi za originalni rad, saopštenje, rad iz istorije medicine i pregled literature do 5.000 reči, a za prikaz bolesnika, rad za praksu, edukativni članak do 3.000 reči; radovi za ostale rubrike moraju imati do 1.500 reči.

Provera broja reči u dokumentu može se izvršiti u programu *Word* kroz podmeni *Tools-Word Count* ili *File-Properties-Statistics*.

Sva merenja, izuzev krvnog pritiska, moraju biti izražena u internacionalnim SI jedinicama, a ako je neophodno, i u konvencionalnim jedinicama (u zagradi). Za lekove se moraju koristiti generička imena. Zaštićena imena se mogu dodati u zagradi.

Naslovna strana. Naslovna strana sadrži naslov rada, kratak naslov rada (do 50 slovnih mesta), puna prezimena i imena svih autora, naziv i mesto institucije u kojoj je rad izvršen, zahvalnost za pomoć u izvršenju rada (ako je ima), objašnjenje skraćenica koje su korišćene u tekstu (ako ih je bilo) i u donjem desnom uglu ime i adresu autora sa kojim će se obavljati korespondencija.

Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

Kratak naslov treba da sadrži najbitnije informacije iz punog naslova rada, ali ne sme biti duži od 50 slovnih mesta.

Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

U donjem desnom uglu naslovne strane treba otkucati ime i prezime, telefonski broj, broj faksa i tačnu adresu autora sa kojim ce se obavljati korespodencija.

Stranica sa sažetkom. Sažetak mora imati do 350 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada. U

izboru ključnih reči koristiti Medical Subject Headings — MeSH.

Stranica sa sažetkom na engleskom jeziku. Treba da sadrži pun naslov rada na engleskom jeziku, kratak naslov rada na engleskom jeziku, naziv institucije gde je rad urađen na engleskom jeziku, tekst sažetka na engleskom jeziku i ključne reči na engleskom jeziku.

Struktura rada. Svi podnaslovi se pišu velikim slovima i boldovano.

Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

Reference se citiraju prema tzv. Vankuverskim pravilima, koja su zasnovana na formatima koja koriste *National Library of Medicine* i *Index Medicus*.

Primeri:

1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prvih šest i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

Slike. Sve ilustracije (fotografije, grafici, crteži) se smatraju slikama i označavaju se arapskim brojevima u tekstu i na legendama, prema redosledu pojavljivanja. Treba koristiti minimalni broj slika koje su zaista neophodne za razumevanje rada. Slova, brojevi i simboli moraju biti jasni, proporcionalni, i dovoljno veliki da se mogu reprodukovati. Pri izboru veličine grafika treba voditi računa da prilikom njihovog smanjivanja na širinu jednog stupca teksta neće doći do gubitka čitljivosti. Legende za slike se moraju dati na posebnim listovima, nikako na samoj slici.

Ako je uveličanje značajno (fotomikrografije) ono treba da bude naznačeno kalibracionom linijom na samoj slici. Dužina kalibracione linije se unosi u legendu slike.

Uz fotografije na kojima se bolesnici mogu prepoznati treba poslati pismenu saglasnost bolesnika da se one objave.

Za slike koje su ranije već objavljivane treba navesti tačan izvor, treba se zahvaliti autoru, i treba priložiti pismeni pristanak nosioca izdavačkog prava da se slike ponovo objave.

Pisma uredniku. Mogu se publikovali pisma uredniku koja se odnose na radove koji su objavljeni u SANAMEDU, ali i druga pisma. Ona mogu sadržati i jednu tabelu ili sliku, i do pet referenci.

Propratno pismo. Uz rukopis obavezno priložiti pismo koje su potpisali svi autori, a koje treba da sadrži: izjavu da rad prethodno nije publikovan i da nije istovremeno podnet za objavljivanje u nekom drugom časopisu, te izjavu da su rukopis pročitali i odobrili svi autori koji ispunjavaju merila autorstva. Takođe je potrebno dostaviti kopije svih dozvola za: reprodukovanje prethodno objavljenog materijala, upotrebu ilustracija i objavljivanje informacija o poznatim ljudima ili imenovanje ljudi koji su doprineli izradi rada.

Troškovi pripreme rada

Svi autori radova, imaju obavezu da pre nego što dobiju potvrdu da će rad biti objavljen u Sanamedu, izvrše uplatu za pokriće dela troškova štampe koja za autora rada iznosi 2500 dinara, a za koautore po 1500 dinara, za svaki prihvaćeni rad. Za autora rada iz inostranstva naknada za štampanje iznosi 40 eura (u dinarskoj protivrednosti po kursu na dan uplate), a za koautore 20 eura. Dodatno će biti naplaćena svaka stranica na kojoj se nalaze slike u boji, po ceni od 30 eura; crno bele slike se ne naplaćuju.

Za sva dalja uputstva i informacije kontaktirajte Uredništvo.

Napomena. Rad koji ne ispunjava uslove ovog uputstva ne može biti upućen na recenziju i biće vraćen autorima da ga dopune i isprave. Pridržavanjem uputstva za pisanje rada za SANAMED znatno će se skratiti vreme celokupnog procesa do objavljivanja rada u časopisu, što će pozitivno uticati na kvalitet i redovnost izlaženja svezaka.

INSTRUCTIONS TO AUTHORS

SANAMED is a medical journal, published since 2006. The journal publishes: original papers, case reports, review articles, letters to the Editor, other articles and information concerned with practice and research in medicine.

Address manuscripts to:
Prim. dr Avdo Ćeranić,
(for Sanamed)
Ul. Palih boraca 52, 36300 Novi Pazar
Email sanamednp2006@gmail.com
www.sanamed.rs

Arrived manuscript is sent to reviewers for expert assessment by the Editorial Board. If reviewers propose changes or amendments, copies of reviews are submitted to authors with a request to enter the required changes to the text or explain its disagreement with the remarks of the reviewer. The final decision of acceptance for publishing is given by Editor in chief.

The journal is published in English, with the summary translated into Serbian.

GENERAL GUIDELINES

Text of the paper should be typed in a word processing program *Word*, written in Latin, double-spaced, only in *Times New Roman* font size 12 points. All margins should be set at 25 mm, and the text should be typed with the left alignment and paragraph indentations of 10 mm, without dividing the words.

The manuscript should be arranged as following: title page, abstract, key words, introduction, patients and methods/material and methods, results, discussion, conclusion, references, tables, figure legends and figures.

Each manuscript component (title page, etc.) begins on a separate page. All pages are numbered consecutively beginning with the title page.

References in the text are designated with Arabic numerals in parentheses, and the order in which they appear in the text.

Manuscript volume. The complete manuscript, which includes title page, short abstract, text of the article, literature, all figures and permisions for them and legends (tables, images, graphs, diagrams, drawings), title page and abstract in English, can have the length up to 5000 words for original paper, report, paper on the history of medicine and literature overview, while for patient presentation, practice paper, educative article it can be up to 3000 words, and other papers can be up to 1500 words.

The word count check in a document can be done in *Word* processor program in submenu *Tools Word Count* or *File Properties Statistics*.

All measurements, except blood pressure, are reported in the System International (SI) and, if necessary, in conventional units (in parentheses). Generic names are used for drugs. Brand names may be inserted in parentheses.

Title page. The title page contains the title, short title, full names of all the authors, names and full location of the department and institution where work was performed, acknowledgments, abbreviations used, and name of the corresponding author. The title of the article is concise but informative, and it includes animal species if appropriate. A subtitle can be added if necessary.

A short title of less than 50 spaces, for use as a running head, is included.

A brief acknowledgment of grants and other assistance, if any, is included.

A list of abbreviations used in the paper, if any, is included. List abbreviations alphabetically followed by an explanation of what they stand for. In general, the use of abbreviations is discouraged unless they are essential for improving the readabillity of the text.

The name, telephone number, fax number, and exact postal address of the author to whom communications and reprints should be sent, are typed at the lower right corner of the title page.

Abstract page. An abstract of less than 180 words concisely states the objective, findings, and conclusion of the studies described in the manuscript. The abstract does not contain abbreviations, footnotes or references.

Below the abstract, 3 to 8 keywords or short phrases are provided for indexing purposes.

The structure of work. All headings are written in capital letters and bold.

Original work should have the following headings: introduction, aim, methods, results, discussion, conclusion, references.

A case report include: introduction, case report, discussion, references.

Review of the literature include: an introduction, subheadings, conclusion, references.

Patients and methods/Material and methods. The selection of patients or experimental animals, including controls is described. Patients' names and hospital numbers are not used.

Methods are described in sufficient detail to permit evaluation and duplication of the work by other investigators.

When reporting experiments on human subjects, it should be indicated whether the procedures followed were in accordance with ethical standards of the Committee on human experimentation of the institution in which they were done and in accordance with the Declaration of Helsinki. Hazardous procedures or chemicals, if used, are described in detail, including the safety precautions observed. When appropriate, a statement is included verifying that the care of laboratory animals followed the accepted standards.

Statistical methods used, are outlined.

Results. Results are clear and concise, and include a minimum number of tables and figures necessary for proper presentation.

Discussion. An exhaustive review of literature is not necessary. The major findings should be discussed in relation to other published works. Attempts should be made to explain differences between results of the present study and those of the others. The hypothesis and speculative statements should be clearly identified. The discussion section should not be a restatement of results, and new results should not be introduced in the discussion.

References. References are identified in the text by Arabic numerals in parentheses. They are numbered consecutively in the order in which they appear in the text. Number of references should not exceed 30, except in the literature review, which is allowed to be to 50.

Avoid using abstracts as references and abstract older than two years are not cited.

References are cited by the so-called Vancouver rules, which are based on formats that use the National Library of Medicine and Index Medicus. The following are examples:

1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first six are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

Tables. Tables are typed on separate sheets with figure numbers (Arabic) and title above the table and explanatory notes, if any, below the table.

Figures and figure legends. All illustrations (photographs, graphs, diagrams) are to be considered figures, and are numbered consecutively in the text and figure legend in Arabic numerals. The number of figures included is the least required to convey the message of the paper, and no figure duplicates the data presented in the tables or text. Letters, numerals and symbols must be clear, in proportion to each other, and large enough to be readable when reduced for publication. Figures are submitted as near to their printed size as possible. Legends for figures should be given on separate pages.

If magnification is significant (photomicrographs), it is indicated by a calibration bar on the print, not by a magnification factor in the figure legend. The length of the bar is indicated on the figure or in the figure legend.

Photographs of identifiable patients are accompanied by written permission from the patient.

For figures published previously, the original source is acknowledged, and written permission from the copyright holder to reproduce it is submitted.

Letters to the Editor. Both letters concerning and those not concerning the articles that have been published in SANAMED will be considered for publication. They may contain one table or figure and up to five references.

Cover letter. The letter signed by all authors must be attached with the manuscript. The letter should consist of: the statement that the paper has not been published previously and that it is not submitted for publication to some other journal, the statement that the manuscript has been read and approved by all the authors who fulfill the authorship criteria. Furthermore, authors should attach copies of all permits: for reproduction of previously published materials, for use of illustrations and for publication of information about pub-

licly known persons or naming the people who contributed to the creation of the work.

Costs of paper preparation

All authors of papers, have obligation, before they receive confirmation that the paper will be published in Sanamed, to pay part of expenses of printing, which is 2500 RSD for author, 1500 RSD for co-authors, for each paper.

For paper author from abroad printing fees are 40 Euro (in Dinar equivalent at the exchange rate on the day of payment), and 20 Euro for co-authors. Additionally will be charged each page with pictures in color, costing 30 Euro; black and white pictures will not be charged.

For any further instructions and information, contact Editorial Board.

Note. The paper which does not fulfill the conditions set in this instruction cannot be set to reviewers and will be returned to the authors for amendments and corrections. By following the instructions for writing the papers for Medical Journal, the time needed for the process of publication of papers in the journal will be shortened, which will have positive impact on the quality and regularity of publication of volumes.

CIP — Каталогизација у публикацији
Народна библиотека Србије, Београд

61

SANAMED / glavni i odgovorni urednik Avdo Ćeranić. — God. 1, br. 1 (2006)– . — Novi Pazar : Udruženje lekara Sanamed, 2006– (Kraljevo : Ofset). — 30 cm

Tri puta godišnje. — Tekst na engl. jeziku. — Drugo izdanje na drugom medijumu: Sanamed (Online) = ISSN 2217-8171

ISSN 1452-662X = Sanamed

COBISS.SR-ID 135154444

ISSN 1452-662X