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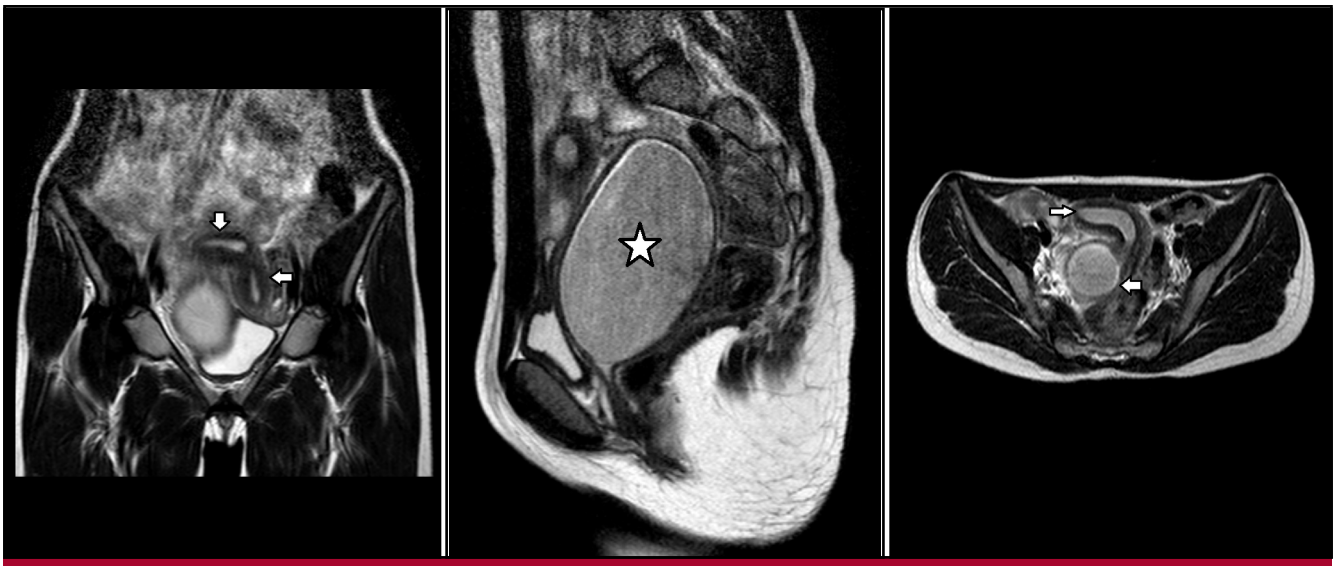

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Dear Colleagues,

We are pleased to have published the second issue of The New Journal of Urology for 2024. This issue includes five (5) original articles and one (1) case report. We believe that all the current articles will be read with interest and these articles are expected to contribute to the literature and serve as a reference for future studies.

The New Urology Journal has been indexed in the TUBİTAK-ULAKBİM TR Index since the first issue of 2011. Our journal is indexed in Google Scholar, Turkish Medline, Turkish Citation Index, SOBIAD, OAJI, Ideal Online Database, EuroPub, J-GATE, and DOAJ databases, EBSCO and InfoBase Index. In addition, the New Journal of Urology is in collaboration with the Orcid and CrossRef DOI systems. The indexing process of our journal in ESCI, Pubmed, and EMBASE continues. The editorial team is very grateful to all the authors and reviewers who have contributed to this issue.

We are aware that this is a painstaking effort, and we cannot thank you enough for it. We request that you submit your articles to The New Journal of Urology, take timely and rigorous action as a referee, and read the articles published in the journal and cite them where appropriate.

Respectfully yours,

Ali İhsan Taşçı
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RESEARCH ARTICLE

Evaluation of Time Perception in Individuals with Lifelong Premature Ejaculation

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Abstract

Objective: Premature Ejaculation (PE) is a common sexual disorder that considerably affects sexual satisfaction, subjective well-being, and quality of life. A clear picture of the pathophysiology of PE has still not been determined. Current research has revealed the involvement of the central nervous system. Alterations in frontal cerebral structures and a discrepancy between the reported and objectively measured intravaginal ejaculatory latency times both point to a possible alteration of time perception. The present study aimed to assess the time perception between individuals with lifelong PE and healthy individuals.

Material and Methods: 24 individuals with lifelong PE and 24 healthy volunteers were recruited. Participants were administered both clinical measures and a time perception test battery including time interval estimation tests and time interval production tests for 4,7,32 and 58-second time intervals.

Results: Lower predictions for 4-second time intervals were found in individuals with lifelong PE than in healthy controls. No differences were found for 7,32 and 58-second time intervals. The Premature Ejaculation Diagnostic Tool scores correlated negatively with the 4-second and 32-second time interval predictions.

Conclusion: The present results indicate a time perception deficit for short intervals in individuals with lifelong PE for the first time. This might be due to a working memory/executive function deficit or disruption of frontal functions on account of impulsivity. A specific deficit in time perception deficit might also occur. Further studies assessing other frontal functions concomitantly are required to draw firm conclusions.

Keywords: Cognitive functions, premature ejaculation, sexual disorders, time perception

INTRODUCTION

Premature Ejaculation (PE) is one of the most common sexual disorders in men that has been characterized by a loss of ejaculatory control and premature ejaculation before expected sexual satisfaction (1). The prevalence of PE has been estimated to be about 20-30% in Türkiye (2). PE results

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in a considerable loss of sexual satisfaction and thereby self-esteem, subjective well-being, and quality of life (1). Since its first definition in 1887, substantial improvement regarding its understanding and more satisfactory treatment outcomes have been reported recently (1,3). While various typologies have been defined, lifelong PE has the best-documented intrinsic pathophysiology. Nevertheless, the exact course and the clear picture of the pathophysiology have not been sketched out thus far (3). A plethora of pathophysiological mechanisms including penile hypersensitivity, 5-HT receptor dysfunction, and anxiety have been identified while numerous others like obesity, sedentary lifestyle, diabetes, and traumatic sexual or emotional experiences have also been depicted to have a possible role (4,5). However, novel insights regarding the contribution of the central nervous system have been gained in the last decade. In animals, various central regions like the medial preoptic area, paraventricular nucleus, periaqueductal grey matter, and lateral paragigantocellular nucleus have been associated with ejaculation (6,7). In these regions, multiple neurotransmitters, especially serotonin, are involved in the processes of ejaculation. In humans, the involvement of the central nervous system in PE is also considered in light of the recent findings. During ejaculation, cranial activity has been indicated to decrease in the medial prefrontal cortex and inferior frontal cortex (8,9). Individuals with PE have also been shown to have functional connectivity alterations in the bilateral medial orbitofrontal cortices, right inferior frontal gyrus, and other cranial brain regions (10–12).

Time perception is a broad term for distinct relevant skills including the ability to measure the time passed between two events, the ability to discriminate the difference between time intervals, etc. which are involved in maintaining numerous daily activities (13). Bearing the wide daily usage in mind, it is not surprising that deficits in some or all aspects of time perception have been revealed in a wide spectrum of neuropsychiatric disorders (14). However, no studies have previously assessed time perception in individuals with lifelong PE. Two main arguments may point to a possible alteration of time perception in individuals with lifelong PE. First, a significant discrepancy between the reported and actual intravaginal ejaculatory latency times has been observed in some of the studies (15,16), but not all of them (17,18). Second, some disruptions have been observed in frontal structures (10,11) which are essentially involved in time perception (19).

The present study aimed to assess the differences in time perception between individuals with PE and healthy individuals. We postulated that specific or generalized alterations in time perception might occur in individuals with PE.

MATERIAL AND METHODS

Design

The present cross-sectional study was conducted in the Department of Urology and the Department of Physiology of the Faculty of Medicine. The study was approved by the local ethical committee (dated 25th December 2022, decision number 91). All participants provided written informed consent. The study procedures complied with the Declaration of Helsinki. Experienced urologists medically examined all participants. No compensation was provided for the participants. The routine medical treatment of the individuals with PE was initiated after completing the study procedures. General mental health status was evaluated with the Patient Health Questionnaire-9 (PHQ-9) (20). The severity of PE was determined with the Premature Ejaculation Diagnostic Tool (PEDT) (21). The International Index of Erectile Function- Erectile Function subscale (IIEF-EF) was utilized to exclude erectile dysfunction (22). Time perception was evaluated with the Time Interval Estimation Tests (TIET) and the Time Interval Production Tests (TIPT).

Participants

Twenty-four treatment-naive individuals with lifelong PE and twenty-four volunteering healthy control subjects were recruited from the urology outpatient clinic. Healthy volunteers were recruited from the hospital attendants. Lifelong PE diagnosis was performed by the International Society of Sexual Medicine-2014 criteria (23). Exclusion criteria were being aged below 18 or above 60, the lack of a heterosexual monogamic partner, less than four sexual intercourses in the last month as at least four sexual intercourses have been suggested to calculate Intravaginal Ejaculatory Latency Time, serious neurologic, psychiatric, or other medical illness, had a history of major pelvic/penile surgery, had retrograde/painful ejaculation or anejaculation, had a sexual partner with sexual dysfunction, or a serious medical illness (24). Participants with a Body Mass Index above 40 and with a PHQ-9 score of above 10 were also excluded. Participants in the lifelong PE group were treatment-naïve, had a mean Intravaginal Ejaculatory Latency Time of less than one minute in the last month, a PEDT score of more than 11, and an IIEF-EF score of more

than 21 to exclude erectile dysfunction. Participants in the healthy volunteer group had a mean Intravaginal Ejaculatory Latency Time of more than one minute in the last month, a PEDT score of less than 11, and an IIEF-EF score of more than 21 to exclude erectile dysfunction.

Instruments

Premature Ejaculation Diagnostic Tool (PEDT): PEDT is a Likert-type self-report diagnostic tool that consists of five practical items to overall determine the presence and degree of PE in males (21). The approximate application duration is 2 minutes. Total scores above 11 correspond to definite PE while total scores of 10 and 11 correspond to probable PE.

International Index of Erectile Function- Erectile Function subscale (IIEF-EF): The International Index of Erectile Function is a comprehensive 6-point Likert-type scale that involves five main sections as follows: Erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. The IIEF-EF is the subscale that chiefly assesses erectile function status (22). The total score of IIEF-EF was calculated with the sum of the first five items and the fifteenth item. Studies indicated its similar validity to the laboratory tests of EF (25). An IIEF-EF score above 21 is probably adequate to exclude EF.

Patient Health Questionnaire-9 (PHQ-9): PHQ-9 is a common diagnostic screening tool to assess general mental status and to screen major depressive disorder. It is a nine-item self-report Likert-type scale that was mainly based on the Diagnostic and Statistical Manual of Mental Disorders-IV criteria. Turkish reliability and validity of the scale were performed in the general population (20). In PHQ-9; total scores between 0-4 correspond to minimal/no depression, total scores between 5-9 correspond to mild depression, total scores between 10-14 correspond to moderate depression, and total scores between 15-21 correspond to severe depression. Individuals with total scores above 10 have 7-13.6 times higher risk of having clinical major depressive disorder (26).

Time Interval Estimation Tests (TIET): In Time Interval Estimation Tests, participants were asked to estimate the duration between two beep sounds that corresponded to "start" and "stop" commands and then tell the duration of the sound verbally. Participants were previously informed that they would be asked to estimate the duration of the time interval. However, counting verbally or using rhythmic body movements was not allowed. Four distinct time intervals (4,7,32 and 58 seconds) were each performed thrice (27,28). Therefore, a total of twelve distinct time intervals were estimated. Interval trials were performed in a randomized order. The averages for each four distinct time intervals were calculated. Then, the average of the reported duration for each interval was divided by the exact duration of the time intervals to calculate the Ratios for each interval.

Time Interval Production Tests (TIPT): In Time Interval Production Tests, participants were asked to produce a previously determined time interval. To this end, participants were asked to give the "stop" command verbally when the previously determined time interval had passed after the "start" command. However, counting verbally or using rhythmic body movements was not allowed. Four distinct time intervals (4,7,32 and 58 seconds) were each performed thrice (27,28). Therefore, a total of twelve distinct time intervals were estimated. Interval trials were performed in a randomized order. The averages for each four distinct time intervals were calculated. Then, the average of the reported duration for each interval was divided by the exact duration of the time intervals to calculate the Ratios for each interval.

Statistical Analyses

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) 25.0 (IBM Corporation, Armonk, NY, USA). Shapiro-Wilk tests were conducted to determine the normality status. All variables except the Ratio of TIPT 4 Seconds were non-normally distributed. Independent Samples T-tests were conducted to compare the normally distributed variables between the lifelong PE and healthy control groups. Mann-Whitney *U* tests were conducted to compare the non-normally distributed variables between the lifelong PE and healthy control groups. A *p*-value below 0.05 was considered significant.

RESULTS

The comparison of the demographic and clinical properties between lifelong PE and healthy control groups is depicted in Table 1. The mean age of the study sample was 32.0 and a significant age difference was found between lifelong PE and healthy control groups ($Z = -4.077$; $p < 0.001$). There were also significant differences in the number of educated years ($Z = -2.661$; $p = 0.008$) and the PEDT scores ($Z = -5.957$; $p < 0.001$), but IIEF-EF scores and the PHQ-9 total scores were similar.

The comparison of the time perception test results is depicted

in Table 2. TIET 4 Seconds Ratios were lower in the lifelong PE group than the healthy control group (t = 2.268; p = 0.029) (Figure 1). There were no significant differences in the TIET Ratios for 7,32 and 52 Seconds.

The PEDT score correlated with the TIET Ratios for 4 Seconds (r = -0.287; p = 0.048) and 32 Seconds (r = -0.303; p = 0.036). There were also correlation trends towards significance between the PEDT score and TIET Ratios for 7 Seconds (r = -0.273; p = 0.060) and 58 Seconds (r = -0.284; p = 0.051).

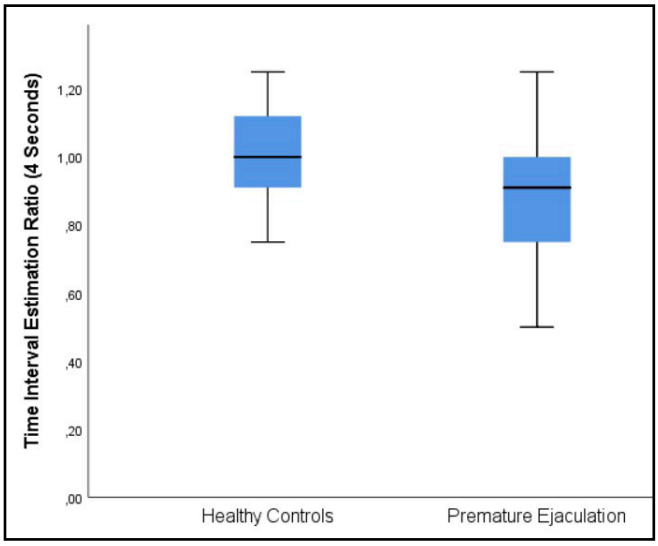

Figure 1. Differences in 4 second (short) time interval between individuals with premature ejaculation and healthy controls. Bars represent standard error.

Table 1. Comparison of Demographic and Clinical Variables Between Individuals with Premature Ejaculation and Healthy Controls

	Variables			
	PE (n=24)	**Healthy (n=24)**	**Z**	**P-values**
Demographic/Clinical Measure				
Age	24.00 (12.50)	36.50 (13.25)	-4.077	**<0.001**
Education (years)	13.50 (4.00)	16.00 (2.00)	-2.661	**0.008**
PEDT	17.00 (7.25)	7.00 (6.75)	-5.957	**<0.001**
IIEF-EF	25.50 (8.00)	24.00 (4.00)	-0.907	0.365
PHQ-9	5.50 (4.50)	6.00 (7.75)	-0.062	0.950

PE: Premature Ejaculation; PEDT: Premature Ejaculation Diagnostic Tool; IIEF-EF: International Index of Erectile Function-Erectile Function; PHQ-9: Patient Health Questionnaire-9. Medians (interquartile ranges) and Z values are shown. Significant p-values are bold.

Table 2. Time Perception Parameters in Individuals with Premature Ejaculation and Healthy Controls

Measures	**PE (n=24)**	**Healthy (n=24)**	**Total (n=48)**	**Z/t**	**p-values**
TIET 4 seconds Ratio	0.885 (0.206)	1.000 (0.230)	0.942 (0.181)	2.268	**0.029**
TIET 7 seconds Ratio	0.900 (0.150)	0.925 (0.130)	0.900 (0.110)	-1.484	0.138
TIET 32 seconds Ratio	0.860 (0.250)	0.900 (0.100)	0.880 (0.120)	-1.566	0.117
TIET 58 seconds Ratio	0.905 (0.160)	0.930 (0.130)	0.910 (0.170)	-1.710	0.087
TIPT 4 seconds Ratio	1.080 (0.120)	1.000 (0.080)	1.040 (0.080)	-1.098	0.272
TIPT 7 seconds Ratio	1.110 (0.410)	1.040 (0.120)	-1.070 (0.250)	-1.061	0.289
TIPT 32 seconds Ratio	1.135 (0.300)	1.075 (0.200)	1.110 (0.290)	-0.827	0.408
TIPT 58 seconds Ratio	1.270 (0.520)	1.150 (0.260)	1.160 (0.430)	-1.469	0.142

PE: Premature Ejaculation; TIET: Time Interval Estimation Test. Mean (standard deviation) and t value for TIET 4 seconds ratio are shown. Medians (interquartile ranges) and Z values for other outcome variables are shown. Significant p-values are bold.

DISCUSSION

The present study intended to assess time perception differences between individuals with lifelong PE and healthy individuals for the first time. Partially consistent with the hypotheses, lower accuracy of the 4-second time estimation was found in individuals with lifelong PE than in healthy controls. Moreover, disease severity as assessed by the PEDT score correlated negatively with the accuracy of the 4-second time estimation. On the other hand, no differences were observed in other time intervals.

The crucial finding of the present study was the alteration of 4-second time interval predictions. Since individuals with PE had lower age than healthy controls, this alteration was not attributable to high age. A variety of reasons might explain this finding. First, this might be due to a slight deficit in working memory/executive functions as there is a significant relationship between time perception and frontal functions (29), and frontal alterations to some extent have been observed in individuals with PE (10,11). Time perception is a multifaceted cognitive function that involves the contribution of numerous cognitive and perceptual processes. Among them, attention and working memory come to the fore which are chiefly maintained by the frontal structures of the brain (29). Auditory and visual inputs are compared with the speed of the internal time clock and integrated with the internal time clock by the prefrontal cortex. This process considerably requires a proper attention/working memory system. However, we did not assess working memory/executive functions and no studies have directly identified a working memory/executive function deficit in individuals with lifelong PE thus far. Nevertheless, previously identified alterations of the frontal structures in individuals with PE might point to a possible attention/working memory deficit (10,11).

Another possible explanation for the lower ratios of the TIET 4 Second test might be impulsivity which might also be associated with the frontal alterations or working memory/executive function deficits. The relationship between short-time-interval estimation and impulsivity supports this notion (30). Even though the neural bases of this assumption have not been exactly identified yet, a theoretical neural model has been suggested that integrates the neural circuits of time perception and impulsivity through the common structures and pathways (30).

Finally, the alteration of time perception in individuals with PE might be also a specific cognitive deficit. Nevertheless, time perception is a complex phenomenon with multiple sub-aspects (13). Thus, further studies are required to draw firm conclusions. It should also be mentioned that we could not determine the order of emergence or the causal link between the PE and the alteration of short-interval time perception since the present study was a cross-sectional study.

A few limitations of the present study should be mentioned. The relatively small sample size, lack of a general cognitive status assessment, and lack of an age-matched control group are the outstanding limitations of the present study.

CONCLUSIONS

To conclude, the present study indicates a significant difference in time perception of a short time interval between lifelong PE and healthy control groups that may point to a specific time deficit or a possible deficit in working memory. However, the present results were not able to confirm these assumptions, and further studies with larger samples are required to draw firm conclusions.

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Ethics Committee: Muğla Sitki Koçman University / Faculty of Medicine (25.12.2022 Decision No: 91).

Author Contributions:

Serkan Aksu: Concept and design, data collection, data analysis and evaluation, writing of the manuscript draft, review of the manuscript draft, statistical analysis, and final approval. Harun Bal, Hüseyin Tarhan, Hasan Deliktaş, Hayrettin Şahin: Concept and design, data collection, data analysis, and evaluation, review of the manuscript draft, statistical analysis, final approval.

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RESEARCH ARTICLE

Liraglutide Attenuates Gentamicin-Induced Nephrotoxicity in Rats by Reducing Oxidative Stress

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Abstract

Objective: Nephrotoxicity is a major complication of gentamicin (GEN), which is widely used in the treatment of severe Gram-negative infections. As we know, treatment with liraglutide has been shown to reduce oxidative stress. Therefore, we evaluated the potential protective effect of liraglutide against GEN-induced nephrotoxicity in rats.

Material And Methods: Twenty-eight rats were randomly divided into four groups: control group (Group 1); rats intraperitoneally injected with GEN (100 mg/kg/day; Group 2); rats treated with GEN plus distilled water (Group 3); and rats treated with GEN plus liraglutide (0.6 mg/kg/day; Group 4). After 15 days, the rats were sacrificed, their kidneys taken, and blood analysis performed. Tubular necrosis, interstitial fibrosis, and inducible nitric oxide synthetase (iNOS) scores were determined histopathologically in a part of the kidneys; malondialdehyde (MDA), reduced glutathione (GSH), E-cadherin and transforming growth factor β1 (TGF-β1) levels were determined in another part of kidneys.

Results: The GSH levels in renal tissue of only GEN-treated rats were significantly lower than others, and the administration of liraglutide to rats significantly increased the level of GSH. The group that was given GEN plus liraglutide had significantly lower MDA, TGF - β1, and E - cadherin levels than that given GEN alone. The rats treated with GEN+liraglutide indicated less severe tubular necrosis and their glomeruli maintained a better morphology compared to the GEN group. iNOS expression was higher in the liraglutide administrated group than the group that applied only GEN.

Conclusion: Liraglutide exerts protective effects on GEN-induced kidney damage by reducing oxidative stress in rat model.

Keywords: gentamicin, liraglutide, kidney

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INTRODUCTION

The kidney is a major organ that plays stunning roles in the human body. The primary duty of the kidney is to sustain the total body fluid volume, its composition, and acid-base balance. Many exogenous pollutants and chemical factors, including drugs, can alter kidney function(1). Gentamicin (GEN), a type of aminoglycoside, is used in the treatment of bacterial infections, but this drug is not renal parenchyma friendly. Nephrotoxicity, estimated to occur in approximately 10-20% of aminoglycoside treatments, is the most important complication of this drug (2) 40 mg/kg b.wt. Compared to the mitochondrial respiratory rates of 7 sham-control rats, State 3 (ADP dependent. Renal free radical production and accumulation causes glomerular congestion and the glomerular filtration rate decreases. This oxidative stress environment due to the rise of free radicals causes acute tubular necrosis(3).

Reactive oxygen species (ROS) are known to be significant mediators of GEN nephrotoxicity(4). In vitro and in vivo studies have shown that substances that reduce reactive oxygen metabolites are protective in GEN-induced renal failure(5). Lipid peroxidation (LPO) interfered with by ROS is a factor of cell destruction in various pathological conditions and indicates cellular damage which is widely used in the treatment of severe Gram-negative infections (6). Reactive oxygen species are important mediators of GEN-induced nephrotoxicity. Because of the strong antioxidant properties of pomegranate extract (PE). Moreover, the activation of proapoptotic and proinflammatory mediators would be stimulated by the superelevation of ROS, thus contributing to kidney damage induced by gentamicin (7).

Various pharmacological substances have been determined to have a potency in avoiding GEN-induced nephrotoxicity(8). Nevertheless, there is currently no clinically encouraging intervention to completely prevent or minimize the effect of GEN-induced nephrotoxicity. The medical world has been dealing with kidney protective antioxidant and anti-inflammatory treatments for a long time. The glucagon-like peptide-1 (GLP-1) analog liraglutide has been reported to reduce high glucose-induced oxidative stress, tumor necrosis factor (TNF) –α, and inflammatory reaction in human endothelial cells(9). Inhibition of protein kinase C (PKC) translocation, nuclear factor (NF) -B activation and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation contribute to the anti-inflammatory and anti-oxidative effects of liraglutide(10). Plasma reactive oxygen compounds are an indicator of oxidative stress. Studies have shown that liraglutide provides significant reductions in plasma reactive oxygen compounds in patients with type 2 diabetes (11). There is also an anti-inflammatory effect of liraglutide. This effect has been demonstrated by experimental animal studies in the brains of rats with Alzheimer's disease and the hearts of diabetic rats (12).

Owing to these influences of liraglutide, in our study, the role of liraglutide in renal damage with GEN was investigated. In the present study, we aimed to find out whether liraglutide has any protective effect against GEN toxicity in an experimental animal study. Since there is no study investigating the protective effect of liraglutide against GEN-induced nephrotoxicity in the literature, our study is the first study on this subject.

MATERIAL AND METHODS

Rats

The experimental study was done on all 28 male Wistar-Albino rats, weighing between 200-300 gr. The rats were housed in clean plastic cages at 20-22°C constant temperature and in a humidity-controlled facility with a stable 12-hour light/dark cycle. During the experiment, the rats were given enough water and rat feed with free access. Ethics committee approval was obtained by applying to the Istanbul University Animal Experiments Local Ethics Committee before the experiment (Approval number: 06/06/2018-147577).

Medicaments

GEN (Gentreks, Bilim Pharmaceutical, Istanbul, Türkiye), and Liraglutide (Victoza®, Novo Nordisk, Plainsboro, New Jersey, USA) were purchased from a random pharmacy. GEN was injected intraperitoneally at a dose of 100mg/kg/day. Liraglutide was administered at a dose of 0.3 mg/kg every 12 hours subcutaneous injection.

Experimental Design

After a quarantine period of seven-day-long, 28 animals were indiscriminately divided into 4 even groups, every consisting of seven rats as follows: (1) control group; (2) GEN injected group for 14 consecutive days intraperitoneally (100 mg/kg/day); (3) GEN plus %0.9 saline-treated group for 14 consecutive days subcutaneously and (4) GEN plus liraglutide treated group (0.6 mg/kg/day liraglutide was administered immediately after injection of GEN) for 14 consecutive days. All rats were processed for 14 consecutive days. After 15 days, the rats were sacrificed by taking blood

from the heart under anesthesia, blood analysis performed, and their kidneys taken. Histopathologically, interstitial fibrosis scores and tubular necrosis were investigated in a part of renal tissues; E-cadherin, reduced glutathione (GSH), malondialdehyde (MDA), and transforming growth factor β1 (TGF-β1) levels were measured in another part of renal tissues. Sodium (Na+), potassium (K+), creatinine, and urea levels were measured as a part of blood analysis.

Biochemical Assays

On day 15, the rats were anesthetized by using xylazine/ketamine (10/50 mg/kg, i.p.) and killed. 24-hour urine collections were acquired in normal cages one day before the rats were killed. Kidney tissues were split into 2 pieces for microscopic inspection and biochemical analysis. Blood was taken from the hearts of rats and Na +, K +, urea, and creatinine levels were measured. MDA, reduced GSH, E-cadherin, and Transforming growth factor beta-1 (TGF-β1) were measured in the renal cortical tissues. For the determination of MDA and GSH in rat kidney tissue, the tissues were weighed, 1/20 (weight/volume) phosphate buffer saline was added (0.1 M / pH 7.4), and homogenized with a tissue homogenizer. Homogenates were centrifuged at 3500rpm for 15 minutes, the supernatants were separated and stored at -80 ° C until the time to be analyzed. MDA levels were assayed spectrophotometrically. MDA is referred to as thiobarbituric acid reagent. MDA was measured with thiobarbituric acid at 532 nm. In the measurement of GSH, the method based on the use of Ellmann's reagent was used and spectrophotometrically measured. Serum creatinine and urea levels were measured by using Beckman Coulter diagnostic kits. Na+ and K+ values were measured by ion-selective electrode method using Beckman Coulter AU5821 autoanalyzer.

Histopathological Examinations

Veterinary pathologist performed the evaluations . Kidney tissue samples obtained from rats were routinely processed, embedded in paraffin blocks, and cut in a manual rotary microtome (Leica RM2255). Sections were investigated under a light microscope (Olympus BX50) after being stained with Hematoxylin & Eosin (H&E). Histopathological evaluation was made according to the degree of tubular damage and the intensity of inflammatory cell infiltration. If tubular damage is less than 25%, mild (1); If the affected tubule ratio is 25-50%, it is medium (2); If more than 50%, it is scored as severe (3). To evaluate inflammatory cell infiltration, 5 random areas were selected at 40x magnification for each kidney section, and scoring for neutrophils and mononuclear leukocytes were done separately. We used Masson's trichrome to assess the degree of interstitial fibrosis. The interstitial area was stained green with Masson's trichrome. Then, an image analyzer was then used (Leica; Leica Micros Imaging Solutions, Cambridge, UK), and 5 pieces were randomly selected from any kidney sample and analyzed. After that, the Banff classification was used to score the degree of interstitial fibrosis and mononuclear cell infiltration (13).

Immunohistochemical Staining

All immunohistochemical evaluations were done double-blinded. Kidney sections taken on positively charged slides for immunohistochemical (IHC) labeling with inducible nitric oxide synthetase (iNOS) primary antibody were stained following the manufacturer's instructions from which the antibody was supplied. Deparaffinized sections were passed through 100, 96, 80, and 70% alcohol series and distilled water, respectively. Heat treatment was applied with citrate buffer solution (pH 6.0) in a microwave oven for 20 minutes at 750W. Then, it was incubated for 10 minutes with a 0.3% hydrogen peroxide solution in methanol to block the endogenous peroxidase activity. Anti-iNOS (PA516855, 1/100 dilution, Invitrogen) antibody was then applied to the sections that were kept at room temperature for 10 minutes by dropping the protein block solution in a humid cabinet and incubating for 90 minutes at room temperature. After the primary antibody incubation, the reaction was completed with a secondary antibody kit (Expose Mouse and Rabbit Specific HRP / DAB Detection IHC Kit, Cat no. Ab80436, Abcam) based on the micro polymer principle. The sections were incubated at room temperature for 10 minutes with Horseradish Peroxidase (HRP) conjugated secondary antibody. It was labeled with diaminobenzidine (DAB). Floor painting with Mayer hematoxylin has been completed. Sections were washed with Tween 20-added phosphate buffer solution (pH 7.4) after all incubation steps until background staining, except between protein blocking and primary antibody steps. IHC staining was examined with a light microscope and the immune reaction was scored according to the ratio of marked tubular epithelial cells and the intensity of staining. If the rate of marked tubular epithelial cells is 0% (0); Light up to 30% (1); 30-60% medium (2); If more than 60%, it was determined as severe (3). Positive reaction intensity was rated as, no reaction (0); light (1); medium (2); severe (3). The final score is determined by multiplying these two scores. Results are expressed as negative (0); mild (1-3); medium (4-6); and strongly positive

(7-9)(14).

Statistical Analysis

The p-value of < 0.05 was accepted as statistically significant. Continuous variables of entire groups were indicated as mean values ± standard deviation (SD). The distribution was examined with the Shapiro-Wilk test. Histopathological data were evaluated using the chi-square test. Biochemical data were analyzed using the Kruskal-Wallis test. In the case of statistical significance between groups, the Mann-Whitney U test was used to determine whether it was significant for the two groups. Bonferroni adjustment for multiple comparisons was applied. P<0.0083 was considered to indicate a significant difference, since the number of groups was four, and the significance level was 5%.

RESULTS

There were no signs of death or visible toxicity in the rats. The biochemical, histopathological, and immunohistochemical outcomes were analogous for the control and liraglutide-treated groups, therefore, we determined to evaluate them indiscriminately and to declare only the control group.

Urinary Volume

It was observed that the highest amount of urine was collected from the GEN-treated rats. This was statistically significant (p < 0.01). This indicated the presence of GEN-induced polyuria. There was no difference in the liraglutide injected group compared to the control group, pointing out the preventive effect of liraglutide towards ATN (Table 1).

Biochemical Variables

The urea and creatinine values were found to be statistically significantly higher in the group of rats treated with GEN alone (p<0.05). With the addition of Liraglutide to the treatment of rats under GEN, a decrease in serum urea and creatinine levels was observed. Na+ and K+ values among the four groups had similarities (Table 1).

When MDA and GSH values were calculated, it was observed that the MDA value in the 4th group and the GSH value in the 3rd group were significantly lower than the other groups (p<0.05). Application of liraglutide after GEN treatment provided a statistically significant increase in GSH values (p < 0.05). When E-cadherin and TGF - β1 values were evaluated, it was observed that they were increased in the group treated with GEN. These values were statistically significant when compared with the control group. TGF - β1 and E - cadherin values decreased significantly after liraglutide injection (p<0.05). The details are shown in Table 2.

Histopathological and Immunohistochemical Results

While mild tubular damage such as granular and vacuolar degeneration was observed in the tubular epithelium in animals belonging to the control group (Figure 1), neutrophil or mononuclear cell infiltration was not detected in the intertubular, interstitial, and perivascular areas. Moderate and severe tubular necrosis, degeneration, dilatation, vacuolization in the tubular epithelium, epithelial hyperplasia, and mild interstitial and perivascular mononuclear cell infiltration were observed in the 2nd and 3rd groups. In the comparison between groups in Table-3, it was seen that tubular necrosis and interstitial fibrosis were more severe in the groups given GEN. In the group given GEN+Liraglutide, a similar histopathological appearance was observed in the control group. Leukocyte infiltration and iNOS were observed to be more severe in the groups that intervened with GEN, and when liraglutide was added to the treatment, similar results were obtained in the control group. (Figure 2 and Figure 3) (Table 3 and Table 4). Epithelial hyperplasia and mononuclear inflammatory cells were observed in the kidney tissues after liraglutide treatment. There was a decrease in the number of degenerative tubules and mononuclear inflammatory cells (Figure 4).

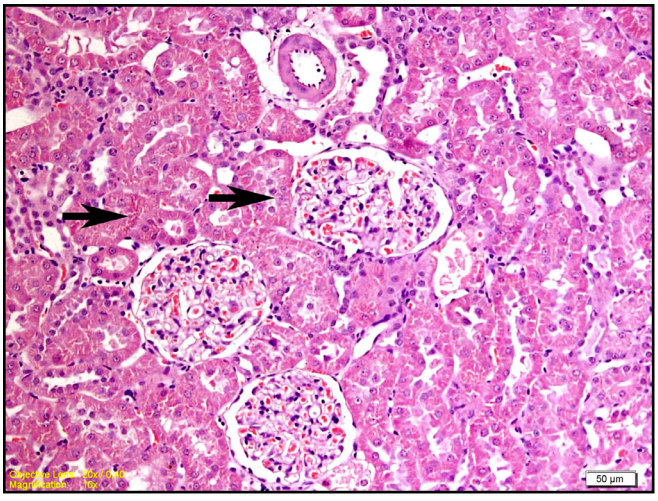

Figure 1. Degenerated, swollen, and granular-looking tubular epithelium (arrows), control group, Bar = 50 µm, H&E

Table 1. Effects of GEN alone and its combination with liraglutide on plasma urea, creatinine, Na^+, K^+, and 24-h urine volume levels in rats.

Parameters	Control (Group 1)	GEN (Group 2)	GEN+Ve (Group 3)	GEN+Liraglutide (Group 4)
Urea (mg/dl)	34±7,1	102±10,3[a]	101±5,1	42±10,2[b]
Creatinine (mg/dl)	0,42±0,1	1,89±0,9[a]	1,83±1,2	0,72±0,4[b]
Na^+ (mmol/L)	138±1,2	139±2,5	138,2±1,3	137±1,6
K^+ (mmol/L)	3,9±0,3	3,9±0,9	4±0,5	3,9±0,2
24-h urine volume (ml)	8,8±1,2	20,3±3,7[a]	21,1±3,2	8,9±1,9[b]

Notes: Values are expressed as mean±SD for seven rats in each group.

Groups: Control, GEN (gentamicin), GEN+Ve (gentamicin+vehicle), GEN+liraglutide(gentamicin+liraglutide)

[a]Significantly different from the control.

[b]Significantly different from the gentamicin group ($p<0.05$).

Table 2. Effects of liraglutide on rat kidney MDA, GSH, E-cadherin, and TGF-β1 levels.

Parameters	Control (Group 1)	GEN (Group 2)	GEN+Ve (Group 3)	GEN+Liraglutide (Group 4)
MDA (μM/mg)	16,5±5,8	26,4±4,3[a]	24,3±2,5	18±4,5[b]
GSH (μg/mg)	3,1±2	2±0,5[a]	1,81±0,9	2,9±0,7[b]
E-cadherin (ng/mg)	0,5±0,2	1,5±0,1[a]	1,5±0,3	0,6±0,3[b]
TGF-β1 (pg/mg)	2,5±0,7	8±1,7[a]	7,6±2,4	3,3±0,5[b]

GSH: reduced glutathione

MDA: malondialdehyde

TGF-β1: transforming growth factor β1

Notes: Values are expressed as mean±SD for seven rats in each group

[a]Significantly different from the control.

[b]Significantly different from the gentamicin group ($p<0.05$)

Table 3. Semiquantitative analysis of tubular necrosis, interstitial fibrosis in control, GEN, GEN + Ve, and GEN + liraglutide groups.

	Tubular necrosis						Interstitial fibrosis			
	n	none	+	++	+++		none	+	++	+++
Control	7	6	1	0	0		6	1	0	0
GEN	7	0	1	2	4		0	1	0	6
GEN + Ve	7	0	0	1	6		0	0	0	7
GEN + liraglutide	7	1	3	3	0		4	1	1	1

n: total number of rats each group , +: mild , ++: moderate , +++: severe tubular necrosis and interstitial fibrosis reported

Acute inflammation findings such as tubuler necrosis and interstitial fibrosis were highest in the ischemia-reperfusion group compared to the other groups.

Table 4. Comparison of leukocyte infiltration and iNOS between groups

	Leukocyte infiltration						iNOS			
	n	**none**	**+**	**++**	**+++**		**none**	**+**	**++**	**+++**
Control	7	6	1	0	0		2	2	2	1
GEN	7	0	1	2	4		1	3	2	1
GEN + Ve	7	0	0	2	5		1	2	3	1
GEN + liraglutide	7	2	3	2	0		1	1	4	1

n: total number of rats each group , +: mild , ++: moderate , +++: severe posivity fibrosis reported

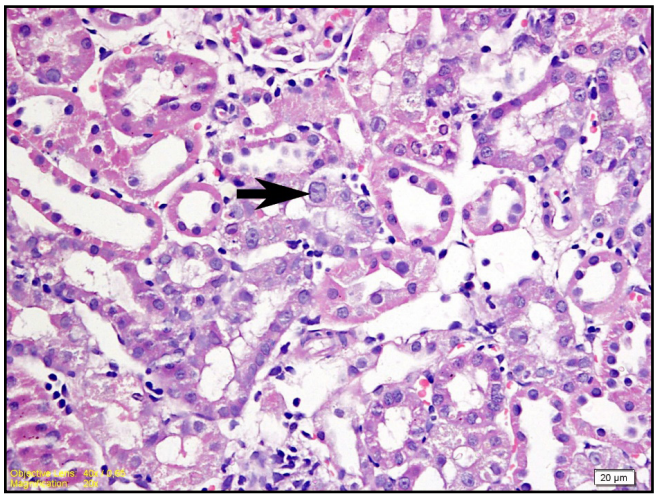

Figure 2. Degenerated, swollen, and granular-looking tubular epithelium, coarse nucleus structure (arrow), GEN group Bar = 20 µm, H&E

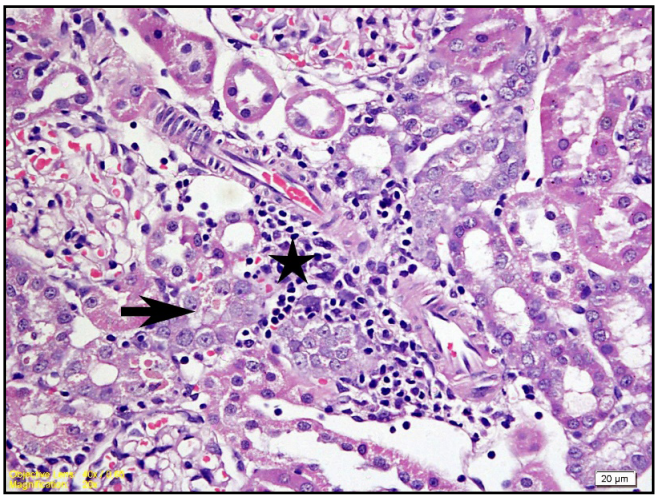

Figure 4. Epithelial hyperplasia areas (arrow), mononuclear inflammatory cells (stars), Gentamicin + Liraglutide group, Bar = 20 µm, H&E.

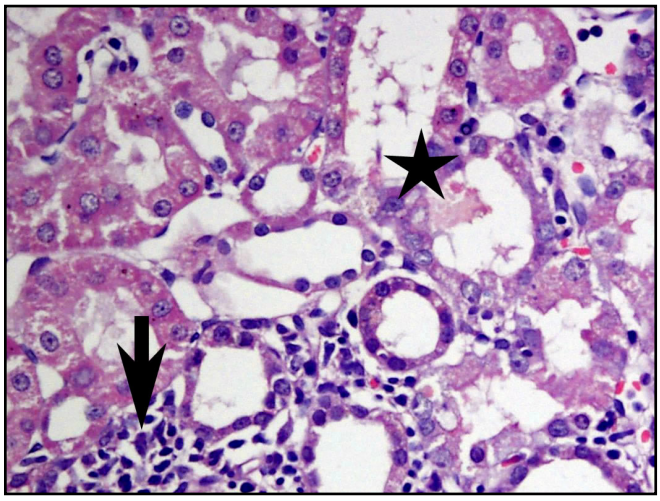

Figure 3. Degenerative tubules (stars), mononuclear inflammatory cells (arrow), GEN group, Bar = 20 µm, H&E

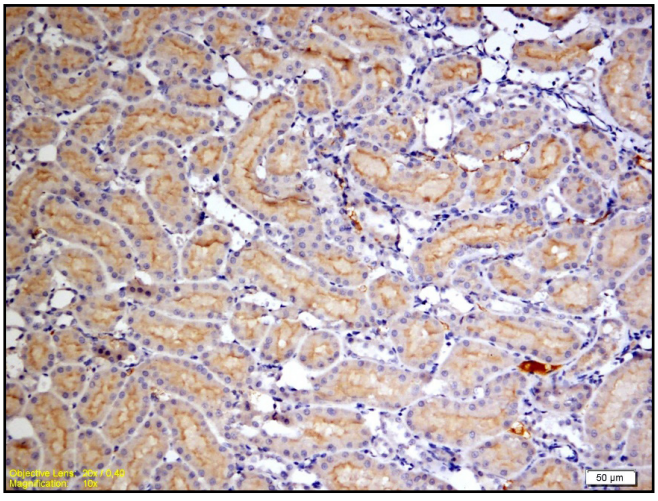

Figure 5. Slight anti-iNOS positive reaction, Control group, Bar = 50 µm, IHC

Varying degrees of positive reaction were found in all groups, including the control group in the immunohistochemical analysis (Figure 5). An anti-iNOS immune positive reaction was observed especially in proximal tubular epithelium. The reaction was rarely observed in the glomerular area. Especially in the gentamicin-applied group, since tubular damage was more severe than in the other groups (Figure 6), the immune reaction was found less due to the absence or necrosis of the epithelium. Tubular damage was moderate in group 4. iNOS expression was higher in group 4 than in the group that was applied only gentamicin (Table 4).

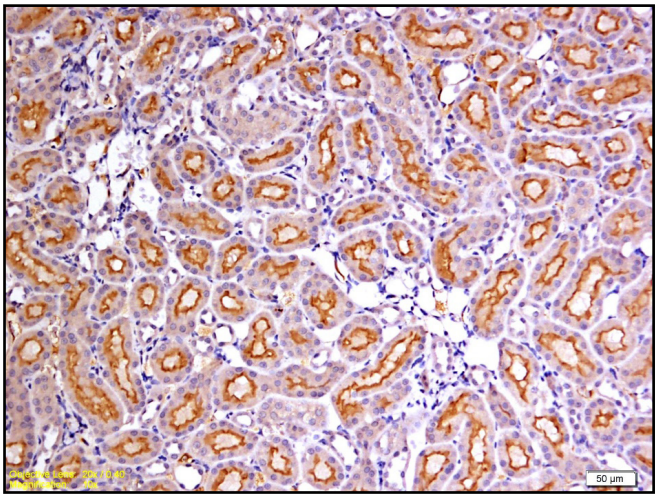

Figure 6. Strong positive anti-iNOS reaction showing intensity in proximal tubules, Gentamicin group, Bar = 50 µm, IHC

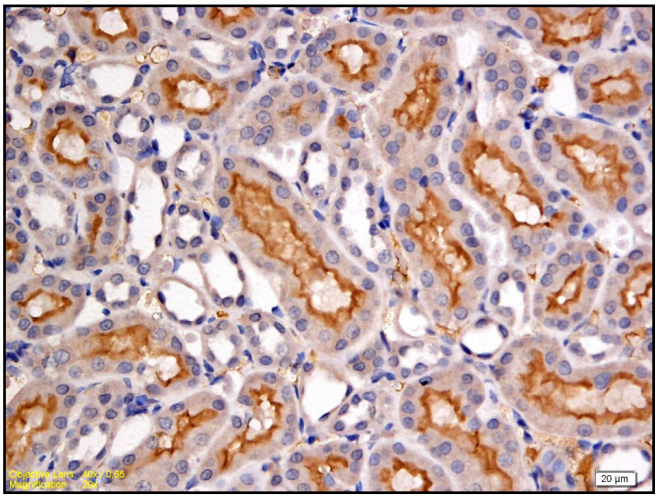

Figure 7. Widespread strong positive anti-iNOS reaction, liraglutide treated group, Bar = 20 µm, IHC

DISCUSSION

The kidneys are sensitive to damage from drugs. Aminoglycosides are one of the antibiotics with proven efficacy against gram-negative bacteria and are used clinically in daily practice, but nephrotoxicity may occur in its use. The tubular effect, triggered by drug accumulation in epithelial tubular cells, constitutes a major part of GEN-induced AKI. Ultimately, gentamicin causes acute tubular necrosis by causing glomerular obstruction, free radical production in the kidney, and decreased antioxidant protection mechanisms which may range from a mere loss of the brush border in epithelial cells to an overt tubular necrosis (15). Tubular cytotoxicity is the consequence of many interconnected actions, triggered by drug accumulation in epithelial tubular cells. Accumulation results from the presence of the endocytic receptor complex formed by megalin and cubulin, which transports proteins and organic cations inside the cells. Gentamicin then accesses and accumulates in the endosomal compartment, the Golgi and endoplasmic reticulum (ER). The use of certain antioxidant agents to reduce or prevent the effect of GEN nephrotoxicity is a reasonable consideration owing to the clear burden of ROS in GEN-induced kidney injury 40 mg/kg b.wt. Compared to the mitochondrial respiratory rates of 7 sham-control rats, State 3 (ADP) dependent (2).

Recently, it has been started to share data that liraglutide reduces oxidative stress caused by high glucose level and tumor necrosis factor (TNF) -α, in endothelial cells(9). Inhibition of PKC translocation, NADPH oxidase activation, and NF -B activation contribute to the anti-inflammatory and anti-oxidative effects of liraglutide(10). Besides, liraglutide reduces the levels of plasma reactive oxygen metabolites, one of the important indicators of oxidative stress (11).

The understanding of GEN nephrotoxicity is quite important clinically; such as in the presence of 1-2 liter urine output per day, an oliguric acute renal failure nephrotoxicity, which can be seen with azotemia(16). In the present study, the significant finding indicating the presence of polyuria due to GEN was that the 24-hour urine volume in the GEN group was the highest amount, while it was not different in the group treated with GEN + liraglutide. It showed the protective role of liraglutide against ATN. Measured creatinine and urea levels after treatment with GEN reflected kidney damage. Normalization of serum creatinine and urea levels after liraglutide administration showed that liraglutide restored renal function by protecting renal cells against the

GEN challenge. In this study, MDA levels, i.e. the indicators of lipid peroxidation of the membranes as a result of oxidative damage as well as both nuclear and mitochondrial DNA (17). Melatonin achieves this widespread protection by means of its ubiquitous actions as a direct free radical scavenger and an indirect antioxidant. Thus, melatonin directly scavenges a variety of free radicals and reactive species including the hydroxyl radical, hydrogen peroxide, singlet oxygen, nitric oxide, peroxynitrite anion, and peroxynitrous acid. Furthermore, melatonin stimulates a number of antioxidative enzymes including superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase. Additionally, melatonin experimentally enhances intracellular glutathione (another important antioxidant, were significantly increased after GEN administration. In parallel with this, GSH levels decreased in the renal tissue after GEN administration. GSH plays an important role in protecting the lipid and protein integrity in the cell membrane, as well as providing great protection from oxidative damage by participating in cellular defense systems (18). In the group treated with GEN+liraglutide, we found decreased MDA levels and increased GSH levels.

iNOS can be produced and detected by inducing secondary messengers in the inflammatory infection process(19). Particularly in the gentamicin-applied group, since tubular damage was more severe than the other groups, the immune reaction was found less due to the absence or necrosis of the epithelium in this study. iNOS expression was higher in the group treated with GEN + liraglutide than in the GEN group. Fibrosis and progressive tubular damage in the renal cortex have been demonstrated in previous studies. In our study, necrosis, degeneration, dilatation, and vacuolization of the tubular epithelium were evaluated histopathologically. All these were most severe in the GEN-treated group. This damage suggested that ROS formed as a result of oxidative stress caused by GEN. The kidney samples of the liraglutide-treated group had quite normal histological features except for slight desquamation and atrophy of the tubular epithelial cells. These findings strongly indicate that liraglutide may have a protective effect against the kidney from GEN-induced injury by improving the oxidant status.

Experimental animal studies are very important in establishing a new treatment modality as they provide the basis for clinical studies. To administer a drug to a person in a pathological situation, several stages are required. Experimental animal studies are one of these stages. In our study, a limited number of data were examined, so it would not be correct to obtain a definite result from a single study, however, when the data obtained from similar experimental studies are evaluated together, a basis for clinical studies can be formed.

This study had some limitations no evidence of long-term effects, the small sample, and the amount of biochemical and histopathological data examined is limited. Besides evaluated morphological semi-quantitative results, quantitative methods were not performed in the present study.

CONCLUSION

The results reported here indicate that liraglutide exerts antioxidant, anti-inflammatory and, antifibrotic effects on GEN-induced renal injury in rats by reducing oxidative stress. The observed protective effects can be attributed to the antioxidant properties of liraglutide. This study can be a good base for more studies aimed at finding the best therapy for this kind of pathology. Even if liraglutide could be protective against renal damage of GEN, it needs further research in larger animal groups.

Conflicts of interest: Authors have no conflicts of interest. The authors have nothing to disclose.

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Ethical Approval: Ethics committee approval was obtained by applying to the Istanbul University Animal Experiments Local Ethics Committee before the experiment (Approval number: 06/06/2018-147577). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions: Conception and design: Degirmentepe RB, Bozkurt M, Data acquisition: Otunctemur A, Yildirim F, Data analysis and interpretation: Erkoc M, Can O, Drafting the manuscript: Degirmentepe RB, Critical revision of the manuscript for scientific and factual content: Gurgen Ozturk H, Eraldemir FC, Hunc F Statistical analysis: Degirmentepe RB

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RESEARCH ARTICLE

Metabolic Risk Factors in Children with Urinary System Stones

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Abstract

Objective: To diagnose, treat, and prevent stone recurrence, it is important to determine the metabolic risk factors that play a role in developing urinary system stone disease in children. This study assessed children with urinary system stones' clinical, radiological, and metabolic characteristics.

Material And Methods: A retrospective study was conducted on the records of pediatric patients who applied to our pediatric outpatient nephrology clinic for various reasons between February 2018 and December 2023 and were diagnosed with urinary system stones.

Results: Of the 122 patients with a mean age of 4.40±4.16 years (1 month-17 years), 63 (51.6%) were boys and 59 (48.4%) were girls. In 61.4% of the children, a family history was identified. The most common presenting symptom was abdominal/flank pain or restlessness (47.5%). In 25.4% of the patients, the stones were ≤3 mm (microlithiasis), and most stones were in the upper system. One or more metabolic abnormalities have been detected during urine analysis for 58.2% of patients. The most frequent metabolic abnormalities were hypercalciuria (20.5%) and hypocitraturia (17.2%). In 74.6% of patients, the size of stones decreased or completely disappeared with medical treatment based on underlying metabolic abnormalities, and in 17.2%, they did not change at all. Only eight (6.6%) patients required interventional procedures.

Conclusion: Metabolic causes should be investigated first in all children with urinary tract stones. Special medical treatments designed to alter metabolism reduce the need for invasive stone procedures.

Keywords: Childhood, Urinary System Stone, metabolic risk factors, hypercalciuria, hypocitraturia

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INTRODUCTION

Urinary system stones are abnormal mineral accumulations anywhere in the urinary system, especially the kidneys. Although it is less common in children than adults, it is common in all ages, including infancy, and is increasingly prevalent (1). It is influenced by prevalence, age, gender, climate conditions, dietary habits, genetic and socio-economic factors, between 1% and 5% in developed countries and between 5% and 15% in developing countries. In adults, it is more common in males, while in children, there is no pronounced male predominance (2). Our country is in an endemic stone range extending from the Balkans to India.

Stone formation is the formation of crystals due to cell degradation at the tubular level for various physical and biochemical reasons. Some underlying anatomical problems that facilitate the development of stones (such as urinary system constraints and vesicoureteral reflux), infections, endocrine, or some metabolic disorders are detected in 75 to 85 percent of affected children (3,4). The vast majority of stones in children are the result of one or more metabolic disorders. An increase in lithogenic solutes such as calcium, oxalate, uric acid, and cystine in the urine and/or a decrease in factors that inhibit stone formation, such as citrate, magnesium, and pyrophosphate, lead to urinary system stones (5-7).

This study aimed to evaluate the clinical, demographic and radiological findings of children diagnosed with urinary system stones in our center and to determine the metabolic causes that cause stones

MATERIAL AND METHODS

The study retrospectively examined the records of 122 children aged 0-18 referred to our pediatric nephrology clinic for various reasons between February 2018 and December 2023. This study was approved by the Local Ethics Committee (decision no: 114, date: 25.01.2024). It was carried out under the principles of the current Declaration of Helsinki and the principles of good clinical practice. The patient's age, gender, age at diagnosis, complaints, and symptoms at presentation, family history of stones, physical examination findings, medications radiological and laboratory findings were obtained from hospital records. Those with endocrine or metabolic disorders were excluded.

During the application period, the urinary system was evaluated by ultrasonography or plain abdominal radiography, which evaluated the location, size, and any anatomical problems of the stone. Stones >3mm in size were defined as urolithiasis, and hyperechoic structures ≤3mm in diameter in the renal calyces were defined as microlithiasis.

To determine the cause of stones, blood urea nitrogen (BUN), creatinine (Cr), sodium (Na), potassium (K), chlorine (Cl), calcium (Ca), phosphorus (P), magnesium (Mg), uric acid, Parathormone, vitamin D, venous blood gases, complete urine analysis and urine culture results were examined. To determine metabolic risk factors that may predispose to stone development, calcium, uric acid, oxalate, cystine, citrate, magnesium, and creatinine levels in spot urine were evaluated and recorded. The metabolites studied from the spot urine sample were standardized by dividing by the urine creatinine level. The results were evaluated according to the values previously stated in the literature (3,8).

Statistical Analysis

Statistical analyses of the study were performed with the Statistical Package for Social Sciences (SPSS), version 26.0 for Windows (SPSS Inc. Chicago, USA) computer package program. Compliance of continuous variables with normal distribution was evaluated using Kolmogorov-Smirnov/ Shapiro-Wilk tests. Variables with normal distribution were given as mean±standard deviation (SD), and variables without normal distribution were given as median (minimum-maximum). Frequency variables were expressed as number (n) and percentage (%). The statistical significance level was accepted as $P<0.05$.

RESULTS

Of the 122 patients who underwent metabolic analysis with the diagnosis of urinary system stone disease, 51.6% (n=63) were male, and 48.4% (n=59) were female, and it was determined that there was no gender difference between the patients ($p>0.05$). The average age at first detection of the stone was 4.40±4.16 years, the age distribution was 1 month-17 years, and the average age of the study period was 5.44 ± 4 years.

Table 1 presents the patients' demographic characteristics and admission findings. Most of the patients (61.4%) had a family history of kidney stones. The most common reason for admission (47.5%) was abdominal/flank pain or restlessness. While restlessness was the most common reason for admission in patients aged five and younger, it was abdominal and/or side pain in patients older than five

years. Urinary system stones were detected incidentally in 11 patients (9%) who had no symptoms suggestive of stones.

In 25.4% of the patients, the stones were ≤3 mm (microlithiasis), and most stones were in the upper system (Table 2). It was determined that there was a significant relationship between stone size and admission findings, such as hematuria and urinary tract infection ($p<0.05$). It was determined that 68.9% (n=84) of the patients had one stone in their urinary system, and 31.1% (n=38) had more than one stone. In our study, mild biochemical abnormalities were detected in a few patients. Three patients (2.5%) had mild hypercalcemia, two patients (1.6%) had mild metabolic acidosis, and one patient (0.8%) had mild metabolic alkalosis. Metabolic disorder was detected in the urine examination of 58.2% of all patients (n=71)(Table 3). While a single metabolic disorder was detected in 65 patients, six patients had more than one metabolic disorder. The most common metabolic cause in our patients was hypercalciuria (20.5%), the second most common was hypocitraturia (17.2%), followed by hyperoxaluria, hyperuricosuria, cystinuria, and hypomagnesuria, respectively.

With medical treatments in addition to adequate fluid intake and salt reduction, the stones in approximately 74.6% (91/122) of the patients shrank or disappeared completely, and the size of 17.2% did not change (Table 4). Stone sizes at the first diagnosis period in patients whose stones disappeared or decreased in size were smaller than in patients whose stones did not disappear. The most common metabolic disorder in these patients was determined to be hypocitraturia (34.1%).

Extracorporeal shock wave lithotripsy (ESWL) was applied to three patients out of a total of eight patients who developed an increase in stone size and/or obstruction in the urinary system due to stones despite medical monitoring and treatments. Stones were removed surgically in three of the other five patients by endourological methods and in two by percutaneous nephrolithotomy. Calcium oxalate stones were detected in five (62.5%) of eight patients, cystine stones were detected in two (25%), and uric acid stones were detected in one (12.5%) of the eight patients who underwent stone analysis.

Table 1. Demographic characteristics of the patients and admission findings

	Number of patients (n)	Ratio (%)
Male/female	63/59	51.6/48.4
Family history of stones	75	61.4
Age distribution at admission		
<1 year	36	29.5
1-5 years	53	43.5
5-10 years	21	17.2
>10 years	12	9.8
Admission findings		
Abdominal/flank pain/ restlessness	58	47.5
Urinary tract infection	24	19.7
Vomiting	15	12.3
Hematuria	14	11.5
Incidental	11	9.0

Table 2. Radiological findings of patients

	Number of patients (n)	Ratio (%)
Size of stone		
≤3 mm	31	25.4
>3 mm	91	74.6
Location of the stone		
Left kidney	40	32.8
Right kidney	33	27.0
Both kidneys	29	23.8
Ureter	12	9.8
Kidney and ureter	8	6.6
Urinary system anomaly		
Hydronephrosis	11	9.0
Horseshoe kidney	1	0.8
Ectopic kidney	1	0.8
Ureterocele	1	0.8

Table 3. Urinary metabolic abnormalities in patients

	Number of patients (n)	Ratio (%)
Patients with metabolic abnormalities	71	58.2
Single metabolic abnormality	65	53.3
Hypercalciuria	25	20.5
Hypocitraturia	21	17.2
Hyperoxaluria	10	8.2
Hyperuricosuria	6	4.9
Cystinuria	2	1.6
Hypomagnesiuria	1	0.8
Multiple metabolic abnormality	6	4.9
Hypercalciuria + Hyperuricosuria	3	2.5
Hypercalciuria + Hypocitraturia	2	1.6
Hypocitraturia + Hyperuricosuria	1	0.8

Table 4. Treatment and follow-up results of patients

Results	Number of patients (n)	Ratio (%)
Patients with no stones detected	68	55.7
Decrease in stone size	23	18.9
Patients whose stone size does not change	21	17.2
Increase in stone size	10	8.2

DISCUSSION

Although urinary system stone disease is relatively less common in children than adults, its frequency has increased in recent years. While a sedentary lifestyle, changing eating habits and inappropriate vitamin use play an important role in this increase, the widespread use of ultrasonography and increased awareness about stones have made diagnosis easier and more frequent (9).

The frequency, etiology, type, content, and location of urinary system stones are associated with geography. The incidence varies worldwide; It is most frequently seen in endemic regions such as Türkiye and Thailand (10). It has been reported that there is a genetic predisposition to the development of urinary system stones and that half of the children with stones have a family history of stones (11). In this study, a family history of stones was found to have a frequency of 61.4%, consistent with the literature.

Urinary system stones are more common in males in adulthood. Male dominance has also been reported in some child studies (12). However, consistent with our study, it is accepted that there is no gender difference in childhood (13,14). In the present study, 51.6% (n=63) of 122 patients were male, and 48.4% (n=59) were female, and there was no statistical gender difference.

Complaints and findings of the patients at admission vary depending on the age of the patient, the location and size of the stone and whether it causes obstruction, the presence of accompanying urinary tract infection (UTI), and the presence of underlying structural or functional genitourinary anomalies (12-15). The most common symptom in children with urinary system stones is flank or abdominal pain. Infants and young children often cannot express the existence, location, and severity of pain and usually present with nonspecific complaints such as restlessness. Apart from pain or restlessness, these patients may experience hematuria, dysuria, urgency symptoms suggestive of UTI, and nausea/vomiting (16). Fifteen to 20% of children with urinary tract stones are asymptomatic, mainly young children whose stones are detected when abdominal imaging is performed for other purposes (17). In our study, 9% of the patients were children whose stones were detected incidentally while examined for another reason. The most common complaints in our remaining patients were abdominal pain, side pain, or restlessness; clinical findings suggestive of urinary tract infection (or history of UTI); nausea/vomiting; and hematuria. The presenting symptoms of our patients were similar to those in previously reported pediatric studies (13,14,18,19).

Twenty to 25% of children with urinary tract stones have a urinary tract infection or a history of infection. Infection may be the primary cause of a stone or may occur along with an underlying urinary metabolic or structural abnormality. Functional or anatomical obstructions of the urinary tract predispose to stasis and infection, possibly encouraging stone formation. Advances in early detection and repair of obstructive uropathies have reduced the incidence of stones due to infections. In this study, one-fifth of the patients had a history of active or previous urinary tract infections at admission, but no one had struvite stones.

Similar to previous studies, our study observed that most urinary system stones (83.6%) were in the upper urinary system (13,14,18,19). None of our patients had bladder stones.

The decrease in the incidence of bladder stones is attributed to changes in eating habits.

In addition to detecting urinary system stones, ultrasonography provides the advantage of anatomical evaluation. In case series of children with urinary tract stones, structural abnormalities (such as hydronephrosis, double collecting system, posterior urethral valve, and bladder anomalies) have been reported in 10 to 25 percent of patients (14,15). Congenital and structural abnormalities accompanied by urinary stasis are associated with kidney stones. Urine stasis paves the way for crystal and stone formation. This study detected structural urinary system anomalies in 14 children (11.4%). Studies from our country reported 3 to 20% of urinary system anomalies (13,14,18).

Most urinary tract stones in children are associated with one or more metabolic disorders. It is important to reveal the underlying metabolic causes in order to apply an effective treatment method. Metabolic studies consist of blood and urine analyses. Hypercalcemia, hyperuric acidemia, high vitamin D, hyperparathyroidism, metabolic acidosis, or alkalosis can be informative in revealing some diseases that may cause urinary system stones. These results guide the diagnosis, diet, and drug treatments of primary diseases (such as renal tubular diseases).

Metabolic etiology in adults is not as common as in children. For this reason, while metabolic evaluation is recommended only for those with recurrent stones in adults, it is recommended when the first stone is detected in children (7,8). The basis of metabolic assessment is measuring the amounts of solutes in the urine that predispose to stone formation. This is calculated by measuring their amounts in 24-hour urine or by the ratio of each solute to creatinine in spot urine and comparing them with normal age (13,14,18,19). In this study, metabolic evaluations were made by spot urine solute/creatinine measurements.

Two mechanisms explain why metabolic factors cause stone formation. First, increased renal excretion of solutes such as calcium, oxalate, uric acid, and cystine or increased urinary concentrations due to low urine volume. This leads to supersaturation and precipitation of the solute, resulting in the formation of crystals that can aggregate into a stone. Second, natural inhibitors of urinary stone formation are scarce, such as citrate, magnesium, and pyrophosphate. Low levels of these inhibitors, especially hypocitraturia, are associated with kidney stones in adults and children. In two case series of children with kidney stones, approximately 90 percent of the patients had at least one metabolic risk factor (7,20). In some studies from our country, Alpay et al. (18) in 87% of patients, Melek et al. (13) in 69.7%, and Taşdemir et al. (14) in 34.8% detected a metabolic cause. Our study found one or more metabolic disorders in 58.2% of the patients.

The most common metabolic abnormality associated with pediatric stone disease is hypercalciuria (21). In most of the studies conducted in our country, hypercalciuria was found to be the most common cause, while in some studies, hypocitraturia was reported more frequently (13,14,18,22). In our study, a single metabolic disorder was detected in 53.3% of the patients, and nearly half of them (20.5%) were hypercalciuria. The rise in excretion of calcium in the urine can be attributed to three mechanisms: increased intestinal absorption (absorptive hypercalciuria), renal tubular calcium reabsorption defect (renal hypercalciuria), and increased bone resorption (resorptive hypercalciuria) (23). Inadequate fluid intake, immobilization, medications such as diuretics and glucocorticoids, excessive vitamin D, and high-salt diets are environmental factors that can cause hypercalciuria.

Other metabolic abnormalities detected in our study were hypocitraturia, hyperoxaluria, hyperuricosuria, cystinuria, and hypomagnesuria, respectively. Citrate is an inhibitor of calcium oxalate and calcium phosphate crystallization. Hypocitraturia is more common in adult patients with idiopathic kidney stones than in children. Although hypocitraturia is mostly idiopathic, a diet rich in animal proteins and low in potassium and plant foods contributes to a decrease in citrate excretion (24).

In our study, hypocitraturia was the second most common cause of stones and was present in 17.2% of the patients. This rate was similar to that of some child studies in our country (19,25). Furthermore, hypocitraturia (34.1%) was the predominant metabolic abnormality observed in our patients whose stones reduced in size or disappeared.

Oxalate, the end product of glyoxylate and ascorbic acid metabolism, is excreted through the kidneys. In our study, hyperoxaluria was the third most frequently detected metabolic disorder. None of our patients had primary hyperoxaluria, which is a genetic-metabolic disease. Idiopathic hyperuricosuria is thought to result from a defect in renal tubular uric acid excretion, and hyperuricosuria is

detected in 2 to 8 percent of children with urinary stones. Although Elmaci et al. (26) and Kara et al. (19) have reported that hyperuricosuria is the most common metabolic disorder in children in our country, the frequency of hyperuricosuria in our study was found to be in line with the frequency reported in the literature. More than one metabolic disorder may occur together in some children with urinary system stones (14,18). In 4.9% of our patients, we have identified more than one metabolic disorder.

As a result, in this retrospective study conducted in children with urinary system stones, there was no gender difference, family history was common, the most common presenting symptom was abdominal/flank pain or restlessness, stones were generally located in the upper urinary system, microlithiasis was found at a considerable rate, anatomical problems could be detected, the most common presenting symptom was abdominal/flank pain or restlessness. It has been determined that the important predisposing factor is a metabolic disorder and that most of the stones shrink and disappear completely with medical treatment.

CONCLUSIONS

Identifying the cause of urinary tract stones and, in particular, detecting underlying metabolic disorders is a major contribution to preventing new stone formation, as well as planning successful diet and pharmacological therapy. We believe it is possible to reduce or eliminate urinary tract stones and prevent their recurrence with early diagnosis of urinary tract stones in children, identification of metabolic disorders, and effective treatment.

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RESEARCH ARTICLE

Inter-Observer Reliability and Reproducibility of CROES, Guy's and STONE Nephrolithometry Scoring Systems for Predicting Percutaneous Nephrolithotomy Outcomes

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Abstract

Objective: To assess inter-observer reliability and reproducibility of CROES, Guy's and S.T.O.N.E. nephrolithometry scoring systems (NSS).

Material and Methods: A total of 128 patients who underwent percutaneous nephrolithotomy (PNL) between January 2019 and January 2021 were included in the study. Calculation of the CROES, S.T.O.N.E, and Guy's NSSs was made by three independent urologists with different academic levels. These were; a very experienced (>500 PCNL cases) endourologist (Rater 1), a urologist who had just finished (>100 PCNL cases) their urology education (Rater 2) and a 3rd year urology resident who had never performed a PCNL operation (Rater 3). All were blinded to the procedure outcomes.

Results: An excellent correlation was found between three raters for Guy and S.T.O.N.E. scoring systems (kappa value 0.810-0.962). However, for the CROES score there is an excellent correlation between Rater 1 and Rater 2, but there were good correlations between Rater 1 vs Rater 3 and Rater 2 vs Rater 3 (kappa values 0.910 and 0.698-0.721 respectively). The highest correlation was between Rater 1 and Rater 2 for Guy score (kappa value 0.962) (Table 3). All intra-class correlations were statistically significant ($p<0.001$). The highest intra-class correlations were seen for the S.T.O.N.E. score (ICC: 0.980).

Conclusion: The present study revealed that all three NSS frequently used in current urology practice have reproducible and reliable results. Additionally, we believe that the application of CROES NSS by more experienced clinicians will be effective in obtaining clearer results.

Keywords: nomogram, scoring systems, percutaneous nephrolithotomy, surgery of renal stones

INTRODUCTION

Percutaneous nephrolithotomy (PNL) is an accepted treatment method for kidney stones greater than 2 cm (1). Success and complications may be affected by many factors including surgeon experience, renal anatomy, and complexity of renal stones. Outcomes of PNL have been reported to have wide ranges in the literature. Therefore, several nephrolithometry scoring systems (NSS) were developed for extensive patient counselling, surgical planning, and assessment of PNL results. Additionally, NSSs are used to

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quantify the complexity of the stone in scientific papers (2).

Recently, three NSSs including the S.T.O.N.E. NSS, the Clinical Research Office of the Endourological Society (CROES) NSS and Guy's NSS are widely used in urology practice (3, 4, 5). After development of an NSS, its predictive accuracy is evaluated by internal and external validation. Although predictive accuracy seems to be the most important factor, simplicity, reproducibility, and achieving the same results with different clinicians are other important properties for an ideal nomogram. Optimally, scores achieved should be similar irrespective of the educational degree and level of expertise of the observer.

Although previous reports validated NSSs in predicting PNL outcomes, none of these studies compared the reproducibility and reliability of the 3 NSSs. In the present study, we evaluated CROES, Guy's and S.T.O.N.E. NSSs for reliability and reproducibility by analysing the scores calculated by 3 raters with different experience level.

MATERIAL AND METHODS

After approval from the Haseki Training and Research Hospital Clinical Research Ethics Committee (Approval Number:280-2023), we performed a retrospective study among patients who underwent conventional PNL from January 2019 to January 2021. Patients with missing data, patients < 18 years old, and patients who did not have pre-operative non-contrast abdominal computed tomography (NCCT) were excluded from the study. Evaluation of stone size, location, and density were evaluated by NCCT. All procedures were performed in the same manner and technique of PNL was described in detail previously. Stone-free status was assessed by NCCT 1-3 months later. Patients who had fragments not larger than 4 mm were considered stone free. Postoperative complications were categorized according to Clavien-Dindo (6).

Nephrolithometry Scoring System Assessment

Calculation of NSSs was made by three urologists with different experience levels (endourologist with >500 PNL, Rater 1; urologist with >100 PNL, Rater 2 and a 3rd year urology resident who had never performed a PNL, Rater 3). All were blinded to the procedure outcomes. CROES NSS (grade 1:0–100, grade 2:101–150, grade 3:151–200, and grade 4:201–350), S.T.O.N.E. NSS (scores between 5 and 13), and Guy's SS NSS (grade 1, 2, 3, 4) were analyzed (3,4,5). Case volume of the center: 500 cases per year.

Statistical Analysis

Statistical Package of Social Sciences for Windows (SPSS) version 20 was used. The compliance of data was evaluated by the Shapiro-Wilk test. Categorical variables were compared with Fisher's exact or Chi-square test. Sample *t* test was used for continuous parameters. Correlation analyses were done using Pearson's correlation coefficient. The Kappa value <0.20 reflects slight agreement, values of 0.21-0.40 are considered fair, 0.41-0.60 moderate, 0.61-0.80 good, and 0.81-1 indicates almost perfect agreement (7). Intra-class correlation was based on a two-way random effects model with type consistency. P <0.05 was considered statistically significant.

RESULTS

A total of 128 patients (86 males and 42 females) were included in the study. According to Rater 1, the mean stone size was 516.5 ± 370.6 mm^2, the mean stone-skin distance was 90.4 ± 24.2 mm and the mean Hounsfield unit (HU) was 1013.8 ± 301.0. The mean operation time and hospitalization time was 80.9 ± 32.7 minutes and 73.2 ± 45.3 hours respectively.

In total, 30 patients (23.4%) experienced complications. According to Clavien Dindo classification complication degree distribution was 6 patients with grade 1, 10 patients with grade 2, two patients with grade 3a and 12 patients with grade 3b. The stone-free status was achieved in 73.4% of patients (94 of 128 patients) (Table 1).

After all scoring systems were calculated by each rater, the Guy scores were 1.9 ± 0.9, 2.0 ± 0.9, and 2.1 ± 0.9, S.T.O.N.E. scores were 7.9 ± 1.4, 8.0 ± 1.4, and 8.8 ± 1.3, and CROES scores 202.9 ± 64.6, 203.7 ± 60.7, 173.1 ± 61.4, respectively according to raters (Table 2).

An excellent correlation was found between the three raters for Guy and S.T.O.N.E. scoring systems (kappa value 0.810-0.962). However, for the CROES score there was an excellent correlation between Rater 1 and Rater 2, but there were good correlations between Rater 1 vs Rater 3 and Rater 2 vs Rater 3 (kappa value 0.910 and 0.698-0.721 respectively). The highest correlation was between Rater 1 and Rater 2 for Guy score (kappa value 0.962) (Table 3). All intra-class correlations were statistically significant (p<0.001). The highest intra-class correlations were seen for the S.T.O.N.E. score (ICC: 0.980) (Table 4).

Table 1. Patient information

Number of Patients		128
Gender	**Female***	42(32.8%)
	Male*	86(67.2%)
Age (years)*		47.2 ± 14.6
BMI (kg/m²)*		27.4 ± 4.9
Operation side	**Right***	70(54.7%)
	Left*	58(45.3%)
Stone size (mm²)*α		516.5 ± 370.6
Stone - skin distance (mm)*α		90.4 ± 24.2
Hounsfield Unit*α		1013.8 ± 301.0
Operation time (minutes)*		80.9 ± 32.7
Hospitalization time (hours)*		73.2 ± 45.3
Stone free status		94 (73.4%)
Complications	**Total***	30 (23.4%)
	Grade 1*	6 (4.7%)
	Grade 2*	10 (7.8%)
	Grade 3a*	2 (1.6%)
	Grade 3b*	12 (9.3%)

*: mean±standard deviation or number (%)
α: According to rater 1
BMI: Body Mass Index

Table 2. Scoring systems according to raters

	Rater 1	**Rater 2**	**Rater 3**
CROES	202.9 ± 64.6	203.7 ± 60.7	173.1 ± 61.4
Guy	1.9 ± 0.9	2.0 ± 0.9	2.1 ± 0.9
S.T.O.N.E.	7.9 ± 1.4	8.0 ± 1.4	8.8 ± 1.3

CROES: Clinical Research Office of the Endourological Society, S.T.O.N.E.: stone size, tract length, degree of obstruction, number of involved calyces and stones' density

Table 3. Kappa correlation coefficient for all raters and scoring systems

Guy Score		
	Rater 2*	**Rater 3***
Rater 1*	0.962 (0.940-0.984)	0.810 (0.760-0.850)
Rater 2*		0.819 (0.775-0.863)
STONE Score		
	Rater 2*	**Rater 3***
Rater 1*	0.948 (0.923-0.973)	0.911 (0.878-0.944)
Rater 2*		0.910 (0.877-0.943)
CROES Score		
	Rater 2*	**Rater 3***
Rater 1*	0.910 (0.879 -0.941)	0.721 (0.671-0.771)
Rater 2*		0.698 (0.646-0.750)

*: 95% confidience
CROES: Clinical Research Office of the Endourological Society, S.T.O.N.E.: stone size, tract length, degree of obstruction, number of involved calyces and stones' density

Table 4. Intra-class correlation among all raters for scoring systems

	ICC	**95% Cl**	**p value**
Guy	0.978	0.970-0.984	***0.001***
STONE	0.980	0.974-0.986	***0.001***
CROES	0.964	0.951-0.973	***0.001***

Cl: confidence interval, ICC: Intra-class correlation
CROES: Clinical Research Office of the Endourological Society, S.T.O.N.E.: stone size, tract length, degree of obstruction, number of involved calyces and stones' density

DISCUSSION

Nomograms in surgical practice are usually used to predict complexity of disease and surgical outcomes; additionally they are used to determine the deviations from normality in internal medicine practice (8, 9, 10). The applicability and effectiveness of nomograms are frequently discussed and researched (11, 12). Researchers mostly focus on the ability of nomograms to predict outcomes; however, questioning of the compatibility and repeatability of the nomograms, and reliability between raters have not been clearly investigated (13). Nomograms can yield different results in terms of accuracy, but it is uncertain whether these differences are due to the nomograms themselves or the clinicians evaluating them. The question of who is the most suitable clinician to evaluate nomograms remains unanswered.

Three NSS are widely used in daily urology practice. In a recent meta-analysis, studies evaluating these three nomograms were examined and all three were stated to be suitable with equal power and accuracy in predicting stone-

free rates (14). However, another important situation is to compare whether these scoring systems always give the same results or not independently of the clinician applying them. In a recent study, the CROES nomogram was applied to their own patient population by 4 independent raters, and they stated that there was excellent agreement between the raters according to the nomogram scores. In the present study, an excellent correlation was determined between Guy's and S.T.O.N.E. NSSs. Experience affected the results most for the CROES NSS. When the correlation was evaluated for the CROES NSS, the results of 2 experienced raters were still perfectly compatible. However, the inexperienced clinician (rater 3) had a lower correlation score compared to both experienced raters. According to the intra-class correlation analyses, the highest correlation was seen for S.T.O.N.E. score and all three NSS achieved a statistical significance.

Analyzing the internal dynamics of these three NSS in detail revealed that there were differences in their natures. In the original article about CROES, stone burden, stone location and stone number are described with figures, but staghorn stone is not defined. The calculation of the score is done by the addition of 6 two-digit numbers marked on a scale. In addition, the size of the stone is obtained by a process that requires a calculator such as "$\text{width}_{max} \times \text{length}_{max} \times 0.785$". When "human error" is taken into account in the application of this score, it involves risks that will prevent obtaining the exact values (15). When the Guy's score is evaluated, the NSS is described with kidney illustrations and the final score is obtained by selecting one of the 4 categories. The lack of requirement for any mathematical operation makes the scoring system the simplest scoring system applied. Our third NSS of S.T.O.N.E. consists of 5 questions, and the answer to these questions comprise numbers from 1 to 4. Scores are obtained by adding these 5 single-digit numbers without the need for a calculator. In light of these explanations, the reason why the first two NSS have excellent correlation and the last one has good correlation between raters is due to the simple-complex nature of these NSSs. It is crucial to emphasize that for a nomogram to be clinically useful, its evaluations must demonstrate consistency across different observers. This consistency ensures that the outcomes are not influenced by subjective human factors, thus maintaining the reliability and validity of the tool. Our results indicate that the evaluations of all three nephrolithometry scoring systems (CROES, Guy's, and S.T.O.N.E.) exhibited high levels of agreement among raters with varying levels of experience. This high degree of similarity underscores the robustness and reproducibility of these nomograms, reinforcing their utility in clinical practice irrespective of the evaluator's expertise.

The retrospective nature of the study inherently introduces potential biases and limits the ability to establish causality. and relatively small patient number in the study could be considered limitations. Secondly, evaluating data for 128 patients according to 3 different nomograms in a short period of time of 1 week may have caused mental fatigue in the authors and affected their evaluation abilities.

CONCLUSION

We have two recommendations. First of all, this analysis could be made with a larger clinician population to achieve better conclusions and prevent mental fatigue of each clinician participating in the study. Secondly, we aimed to provide a guide for who is eligible to analyse nomograms but we did not evaluate whether the analysis could be made fully by artificial intelligence (AI) to prevent human error completely. We often see studies about AI in the field of radiology which may be subject of further studies in urology field (16).

The present study revealed that all three NSS have reproducible and reliable outcomes in prediction of PNL outcomes. Additionally, we found that the use of CROES NSS by more experienced clinicians will be effective in obtaining more clear results.

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RESEARCH ARTICLE

The Role of Hematologic Parameters in Predicting Orchiectomy for Testicular Torsion

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Abstract

Objective: Testicular torsion is an urological emergency that requires early intervention. When torsion is diagnosed late, the possibility of organ loss increases. In this study, we investigated the role of preoperative hematological parameters in predicting orchiectomy.

Material and Methods: A total of 136 patients who had undergone surgery due to testicular torsion were included in this study. Patients are divided into two groups as orchiectomy (n=48) and testicular fixation (n=88). The groups were compared with age, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), platelet count (PLT), mean platelet volume (MPV), neutrophil count, lymphocyte count, symptoms of duration, side and the degree of torsion.

Results: The mean age was 18.2 ± 9.6 in orchiectomy group and 17.2 ± 6.1 in testicular fixation group (p=0.569). The symptoms of duration was statistically higher in orchiectomy group (57.4±35.7 vs. 8.7±7.4 (p=0.001)). NLR was 5.03±2.93 in orchiectomy group and 6.72±3.51 in testicular fixation group (p=0.005). MPV was found to be significantly higher in the orchiectomy group (p=0.001). There were no differences between the groups in terms of the PLR (p=0.137), PLT (p=0.251), neutrophil count (p=0.309) and lymphocyte count (p=0.895). In multivariate analysis, the degree of torsion and the duration of symptoms were found to be predictive for orchiectomy (p=0.003, p<0.001).

Conclusion: Many studies have reported that preoperative haematological parameters predict orchiectomy. However, no predictive factor was found in our study.

Keywords: Testicular Torsion, Orchiectomy, Hematological Parameters.

INTRODUCTION

Testicular torsion is an emergency condition characterized by the rotation of spermatic cord around itself and has incidence of 1/4000 of men under the age of 25 (1). As a result of torsion, testicular blood supply is impaired, ischemia occurs and the risk of infertility increases (2). The possibility of testicular ischemia is depends on the duration of symptoms (1). It is diagnosed with physical examination and scrotal doppler ultrasonography. If intervention occurs within the first 6 hours after the onset of torsion, the possibility of undergone orchiectomy decreases, whereas if it continues longer than 12 hours, the orchiectomy rate increases dramatically (3,4). 31-41% of cases result in orchiectomy and it may cause severe consequences such as decreased fertility rate, hormonal

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dysfunction and pshychological trauma (5).

The most important parameters that affecting recovery is the onset of symptoms and depends entirely on the information given by patient. Patients are mainly at pediatric ages and the time of onset of symptoms is subjective (6). Besides that, it prolongs the process of application to clinic because the teenagers do not consent to genital area examination (7).

Some studies in the literature have indicated that haematological parameters may be useful in predicting testicular viability in the presence of testicular torsion. Neutrophil-Lymphocyte Ratio (NLR) is a simple blood test result that has proven predictive role in many disorder and has become more popular lately. It is an inflammation parameter and has previously been used to differentiate between testicular torsion and epididymitis (1,8). In this study, we aimed to investigate the results of hematological parameters in predicting the orchiectomy in testicular torsion in a large population.

MATERIAL AND METHODS

The patients' data who had undergone orchiectomy or testicular fixation due to testicular torsion between January 2013 and January 2023 were analyzed retrospectively. The patients' age, side, duration of symptoms, medical and surgical history, the degree of torsion and preoperative hematological parameters were evaluated. The patients with the history of previous scrotal surgery, diagnosed epididymitis within 1 month and neonatal torsion were excluded. Patients who were initially diagnosed preoperatively with torsion but subsequently found not to have torsion during exploration were excluded from the study. one hundred-thirty six patients who diagnosed testicular torsion via both physical examination and scrotal doppler ultrasonography were included the study. In the patients, the testicle which appeared ischemic during scrotal exploration, was detorsioned and warm physiological saline was applied and waited for 15 minutes. Orchiectomy or testicular fixation was performed according to reperfusion. A complete blood count analysis was conducted preoperatively on all patients, with the recorded values for lymphocyte count, neutrophil count, platelet count (PLT), and mean platelet volume (MPV). The NLR and platelet-to-lymphocyte ratio (PLR) were subsequently calculated.

This study was achieved accordance to Helsinki Declaration (193/2013), approved by our Institutional Review Board (2020/514/184/2), and written informed consent was obtained from all patients before the treatment.

Statistical analysis

For descriptive statistics, mean, standard deviation and frequency were used. The Kolmogorov-Smirnov test was used to test the distribution of the variables. Quantitative data were compared using independent samples t-test and Mann-Whitney U-test. Chi-Square was used to compare qualitative data. Multivariate logistic regression analysis was performed to investigate variables which might be predictive for orchiectomy. Variables included symptom duration, testicular torsion angle, NLR, PLT, PLR, MPV. SPSS 26.0 was used for statistical analyses.

RESULTS

A total of 88 patients who had undergone testicular fixation and 48 patients who had undergone orchiectomy were compared. The demographic data of the patients and perioperative parameters are given in Table 1. The mean age was 18.2±9.6 for orchiectomy group and 17.2±6.1 for testicular fixation group (p=0.569). No differences were observed in the side and previous inguinal surgery history between the groups. (p=0.076, p=0.770 respectively).Time to surgery was significantly higher in the orchiectomy group (57.5±35.7 vs. 8.7±7.4) (p=0.001). Degree of torsion is statistically higher in the orchiectomy group (p<0.001).

No statistically differences were observed between the groups with regard to the PLT (p=0.251), neutrophil count (p=0.309) and lymphocyte count (p=0.895) (Tablo-2). PLR value was similar in both groups (149.8±60.6 vs.178.4±105.4 respectively) (p=0.137). NLR was 5.03±2.93 in orchiectomy group and 6.72±3.51 in testicular fixation group. It was found to be significantly higher in testicular fixation group (p=0.005). MPV was found to be significantly higher in orchiectomy group than testicular fixation group (p=0.001) (8.81±1.1, 8.19±0.94, respectively). In multivariate analysis, while the degree of torsion and the duration of symptoms were found to be predictive for orchiectomy preoperatively; MPV and NLR didn't have predictive roles for orchiectomy (Table-3).

Table 1. Patient characteristics and peroperative data

	Orchiectomy mean±Sd / min-max	Orchiopexy mean±Sd / min-max	p value
Age	18.2 ± 9.6 / 4-34	17.2 ± 6.1 / 3-36	0.569
Laterality: Right (n/%) Left (n/%)	25 (52) 23 (48)	32 (36) 56 (64)	0.076
Symptom duration (h)	57.5 ± 35.7 / 3-160	8.7 ± 7.4 / 2-48	**0.001**
Previous inguinal surgery (n/%)	8 (16)	13 (14)	0.770
Testicular torsion angle (n/%)			**<0.001**
0-180	4 (8)	38 ((43)	
-360	21 (44)	37 (42)	
-540	11 (23)	9 (10)	
-720	9 (19)	4 (5)	
-1080	3 (6)	0	

Table 2. Hematologic parameters of the study groups

	Orchiectomy mean±Sd / min-max	Orchiopexy mean±Sd /min-max	p value
Lymphocyte (10^3/μL)	1.99 ± 0.73 / 6.8-19.4	1.97 ± 1.12 / 5.3-29.7	0.895
Neutrophil (10^3/μL)	8.8 ± 2.9 / 3.5-16	9.5 ± 3.6 / 2-19.3	0.309
PLT (10^3/μL)	266.0 ± 52.2 / 165-367	284.4 ± 87.7 / 140-550	0.251
NLR	5.03 ± 2.93 / 1,2-13	6.72 ± 3.51 / 0.8-16.2	**0.005**
PLR	149.8 ± 60.6 / 69,7-327	178.4 ± 105.4 / 46.9-507.7	0.137
MPV(μm^3)	8.81± 1.1 / 6.9-11.2	8,19± 0,94 / 6.5-10.9	**0.001**

PLT:platelet count; NLR:neutrophil to lymphocyte ratio; PLR:platelet to lymphocyte ratio; MPV:mean platelet volume

Table 3. Multivariate analysis results

	Odds ratio	%95 Cl	P value
Symptom duration	0.833	0.757-0.917	**<0.001**
Testicular torsion angle	0.199	0.070-0.568	**0.003**
MPV	0,577	0.169-1,968	0,380
NLR	1.025	0.601-1.749	0.959
PLR	0.996	0.974-1.019	0.767
PLT	0,997	0.980-1.015	0.764

PLT:platelet count; NLR:neutrophil to lymphocyte ratio; PLR:platelet to lymphocyte ratio; MPV:mean platelet volume

DISCUSSION

In this study, it was investigated whether hematological parameters had a role in predicting orchiectomy in patients admitted due to testicular torsion.

Complete Blood Count (CBC) is a rapid test used routinely before the surgery. Various parameters in the CBC is used in the diagnosis and follow-up of many diseases (9). Although these parameters vary in acute or chronic cases, they can provide important information about the course of diseases. These parameters have recently been examined in testicular torsion, which is an acute inflammatory condition. Numerous studies have reported that hematological parameters can be used in the differential diagnosis of testicular torsion (2,10).

In a study that published in 2015, 75 patients diagnosed with torsion were compared with 56 healthy male patients. In this retrospective study, NLR, PLR and PLT values were higher in TT group. Besides that, NLR was found to be higher in patients with duration of symptoms more than 12 hours (2). In a study published in 2019, the data of 60 patients who had undergone surgical exploration with a diagnosis of torsion were retrospectively examined and orchiectomy was performed in 38 of these patients, testicular fixation was performed in 22. In this study, NLR ($p<0.001$), PLR ($p=0.01$) and WBC ($p=0.01$) values were found to be significantly higher in orchiectomy group but PLT was similar between the two groups ($p=0.28$). It is reported that NLR and the duration of symptoms has a predictive role (11). Chen et al. compared the results of 43 patients who had underwent orchiectomy, 124 patients who underwent orchiopexy, and 100 control patients, retrospectively. NLR and PLR values were found to be statistically higher in orchiopexy group but PLT value was found to be similar ($p=0.204$) (12). Meder et al. compared orchiopexy (n=61), orchiectomy (n=27) and the control groups (n=56). NLR was found to be statistically lower in control groups but there was no difference between orchiectomy and orchiopexy groups (13). In our study, NLR was found to be statistically higher in orchiectomy group. However, degree of torsion and symptom duration were found to be predictive, while NLR was not found to be predictive in multivariate analysis.

MPV is an indicator of platelet activation. Studies shown that MPV can be used in the diagnostic process of various inflammatory and vascular disorders. In a study, Çiçek et al. compared TT and healthy control group. MPV was found to be higher in TT group (8.3 ± 1.2 vs. 7.1 ± 0.8, $p<0,001$) (2). In another study which they compared the hematological parameters of 19 patients with testicular torsion, MPV found to have predictive role of testicular viability in patients with symptoms lasting less than 6 hours (14). In a retrospective study, He et al. compared orchiopexy (n=54) and orchiectomy (n=58) patients and it is found that MPV value was significantly higher in orchiectomy group. MPV was reported to be a predictive parameter in predicting orchiectomy in TT (10). In a study reported by Güneş et al, testicular torsion patients and healthy patients as control group were compared and no significant difference was found between the groups in terms of MPV (2). In another study, patients who had undergone orchiectomy and orchiopexy were compared and no difference was found between the groups in terms of MPV (12). In the present study, MPV value was found to be higher in orchiectomy group. However, it was not found to be predictive for orchiectomy in multivariate analysis. When all these findings are evaluated, the role of MPV in diagnosing torsion and predicting orchiectomy is still controversial.

The most important predictive parameter for testicular viability in testicular torsion is duration of symptoms. In some studies, it was found that the degree of testicular rotation was also predictive of testicular viability (10,12). Similarly, in our study, symptom duration and degree of testicular rotation were significantly higher in the orchieotomy group. In the regression analysis, it was found to be a predictive factor for orchiectomy.

We have two limitations in this study. First, the nature of study is retrospective. Torsion is an emergency disease that requires urgent interventation, so the patients were examined by different surgeons and scrotal doppler ultrasound was performed by different radiologists. Secondly, other inflammatory parameters such as sedimentation and CRP could not be evaluated for some patients and could not be included in this study.

CONCLUSIONS

CBC is a cheap, rapid simple blood test. Hematological parameters may be an independent variable for diagnosing testicular torsion and predicting testicular ischemia. However, the definitive diagnosis is still performed with scrotal exploration and the experience of the surgeon. Prospective studies with large population are essential to reaching certain conclusions.

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CASE REPORT

Zinner Syndrome Versus Herlyn-Werner-Wunderlich Syndrome; Rare Congenital Genitourinary Malformations and Literature Review

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Abstract
Zinner Syndrome (ZS) and Herlyn-Werner-Wunderlich Syndrome (HWWS) are congenital genitourinary anomalies accompanied by ipsilateral renal agenesis. These syndromes, which can cause symptoms such as infertility, pelvic pain, and bladder irritation, can be diagnosed by digital rectal examination, transrectal and abdominal ultrasonography (US), Computer Tomography (CT) and more ideally Magnetic resonance imaging (MRI). Similar physiopathological processes are observed in both syndromes and urogenital malformations accompany renal agenesis. We aimed to discuss the three cases of ZS in men and two HWWS cases in women, which are rarely observed in the literature.

Keywords: Zinner syndrome, Herlyn-Werner-Wunderlich syndrome, Seminal vesicle cysts, renal agenesis, mullerian duct anomaly, blind hemivagina, uterus didelfis

INTRODUCTION

Zinner syndrome (ZS) is an upper urinary tract malformation first described in 1914. It is characterized by unilateral renal agenesis, ipsilateral seminal vesicle occlusion and ipsilateral ejaculatory duct obstruction (1). Herlyn-Werner-Wunderlich syndrome (HWWS) is a rare variant of mullerian canal anomalies, occurring with blind hemivagina, uterine didelfis and unilateral renal agenesis triad (2).

A developing fetus is constantly under hormonal regulation. In the first phase of development, both XX and XY channels are indistinguishable. In the next stage, depending on whether there are testosterone and Mullerian inhibitory factor, it differs as Wolfian duct or Mullerian duct

Similar physiopathological processes are observed in both syndromes and urogenital malformations accompany renal agenesis. We aimed to discuss the three cases of ZS in men and two HWWS cases in women, which are rarely observed in the literature. Although there is no definitive information about the etiology and pathogenesis of HWWS, it is associated with anomalies formed by the paramesonephric (Müller) and mesonephric (Wolff) ducts (3).

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HWWS is a developmental anomaly that is accompanied by ipsilateral hemivagina obstruction and renal agenesis and is not a genetic disorder. Diagnosis can be made through non-invasive procedures such as physical examination methods and radiological examination. Most patients with HWW syndrome need to be treated surgically. The treatment plan should be made according to the affected anatomical disorder of each patient. Therefore, a detailed and comprehensive evaluation should be made before surgery.

Case- 1. The first case was a 28-year-old male patient who was admitted to the urology outpatient clinic with infertility. After physical examination and medical history, spermiogram was performed with suspicion of testicular dysfunction. Ultrasonography (US) examination was performed due to detection of azoospermia in spermiograms performed at two different times. Furthermore, the semen volume was 0.8 cc, and the pH was 7.2 in both tests. A cystic lesion was detected in the right seminal vesicle, but it could not be detected in the right kidney (agenesis). No significant abnormality was detected in the hormone tests performed.

Computed tomography (CT) revealed right renal agenesis (**Fig. 1.a.b**). The testicular vein calibration draining into the left renal vein was slightly thin and increased vascularity due to pelvic congestion on the left side of the pelvic region were observed **(Fig. 1.c)**. There was also cystic tubular dilatation at the seminal vesicle level **(Fig. 1.d).** In MRI examination; at the seminal vesicle localization, a cystic tubular hyperintense appearance was observed, and the tubular cystic structure on the right was seen extending towards the superior. There was a cystic nodular structure in the central of prostate that caused obstruction at the ductus ejaculatorius level (**Fig. 2**). In addition, these cystic structures were found to be complicated by hemorrhage in T1 Weight images (**Fig. 3**).

Case- 2. In the routine US examination performed in a 36-year-old male patient who was followed up for Acute myeloid leukemia(AML), cystic dilated tubular structures with a maximum diameter of 30 mm were observed in the seminal vesicle localization. Further radiological examinations were performed after the patient described that he had anejaculation and had recurrent pelvic pains. In contrast-enhanced CT examination; right renal agenesis was observed and a cystic lobular lesion was detected at the level of the seminal vesicle (**Fig. 4.a.b).**

Case-3. In another case, dilated seminal vesicles and renal agenesis were observed in MRI examinations performed at the outpatient clinic where he admitted with similar complaints. MRI examination shows dilated seminal vesicles on coronal fat-suppressed T2 and T2-weighted images (**Fig. 5.a.b.c**).

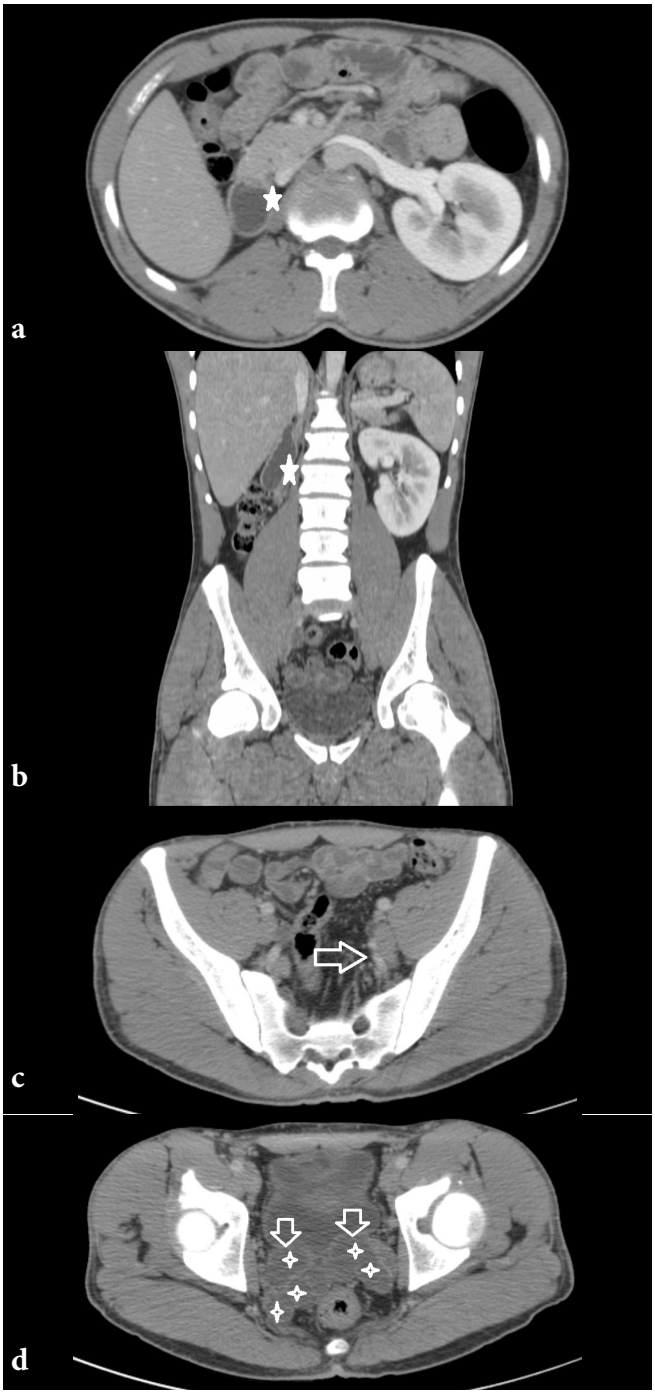

Fig. 1. In CT examination; Right kidney agenesis is observed **(a-b).** In the left side of the pelvic region, there is an increase in pelvic vascularity **(c)** and an expansion in the cystic tubular structure at the level of the seminal vesicle **(d).**

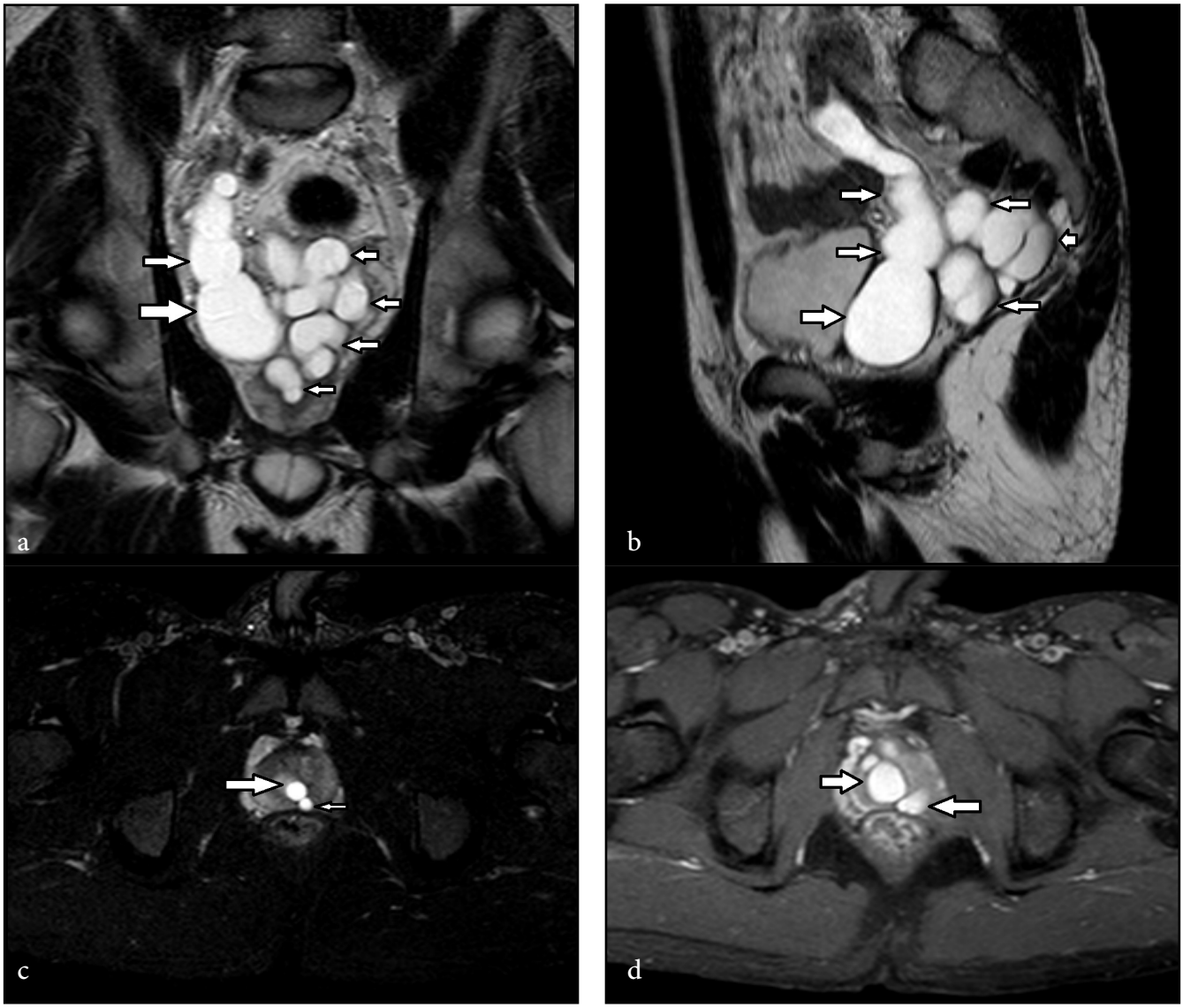

Fig. 2. In the seminal vesicle lobe, T2 Weight images show a cystic tubular hyperintense appearance **(a)** and the tubular cystic structure extends towards the superior on the right **(b).** In the prostate central section, a cystic nodular structure that causes obstruction at the level of ductus ejaculatorius is observed **(c-d).**

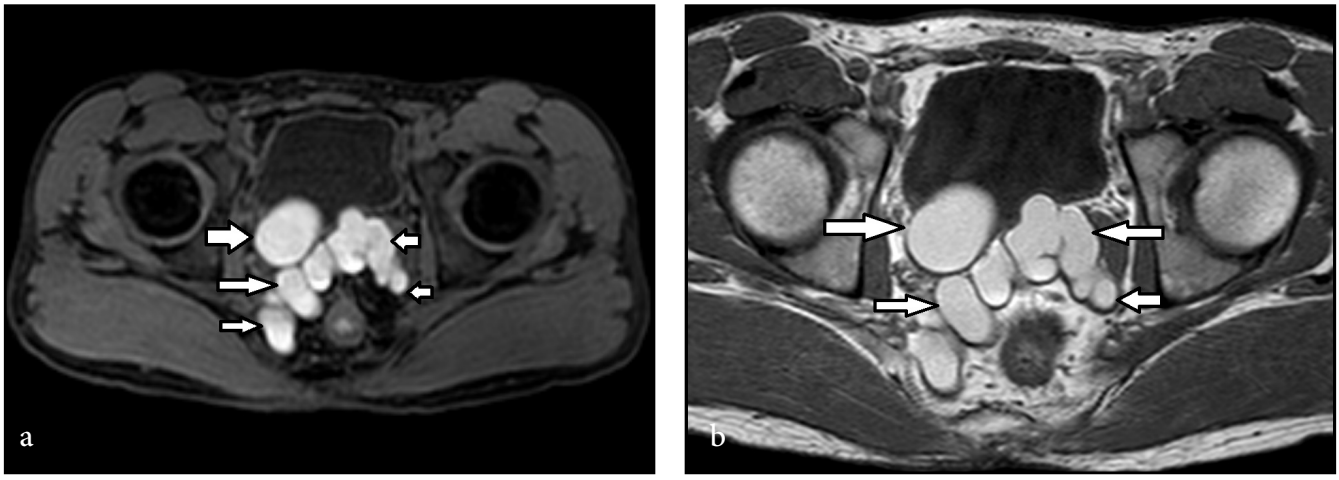

Fig. 3. These cystic structures are observed to be complicated by hemorrhage in T1 Weight image **(a)** and fat-sat **(b)** images.

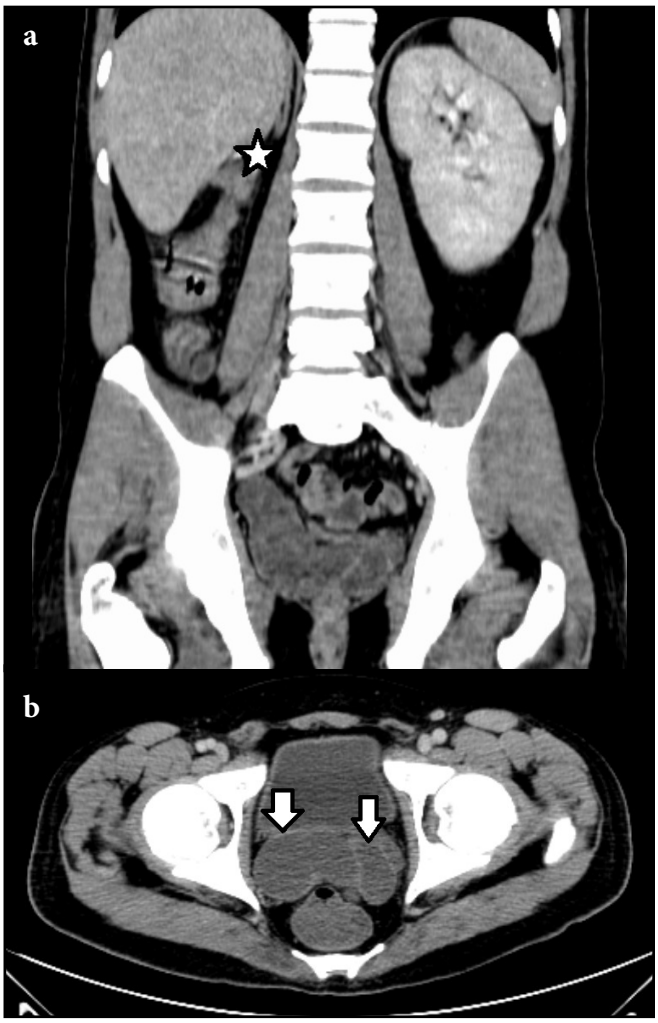

Fig. 4. In the CT examination of 36 y.o male patients; On the right, renal agenesis was observed**(a)** and a cystic lobular lesion was observed at the level of the seminal vesicle **(b).**

Case-4. 14 years-old female petient admitted with recurrent abdominal pain and irregular menstrual complaint. Imperforate hymen was detected on physical examination. Thereupon, pelvic US and MRI were examined for further examination.

In ultrasonography examination; the right kidney was not observed in place (right renal agenesis) and endometrial cavity filled with a large hemorrhagic collection extending into the cervix was observed in the pelvic area.

In MRI examination; endometrial cavity showing two separate endometrial bands surrounded by separate muscle layers(uterine didelphys) and the right of this, obstructed blind hemivagina was detected was observed in coronal T2-weighted image (**Fig. 6.a**). In T2-weighted sagittal images; It

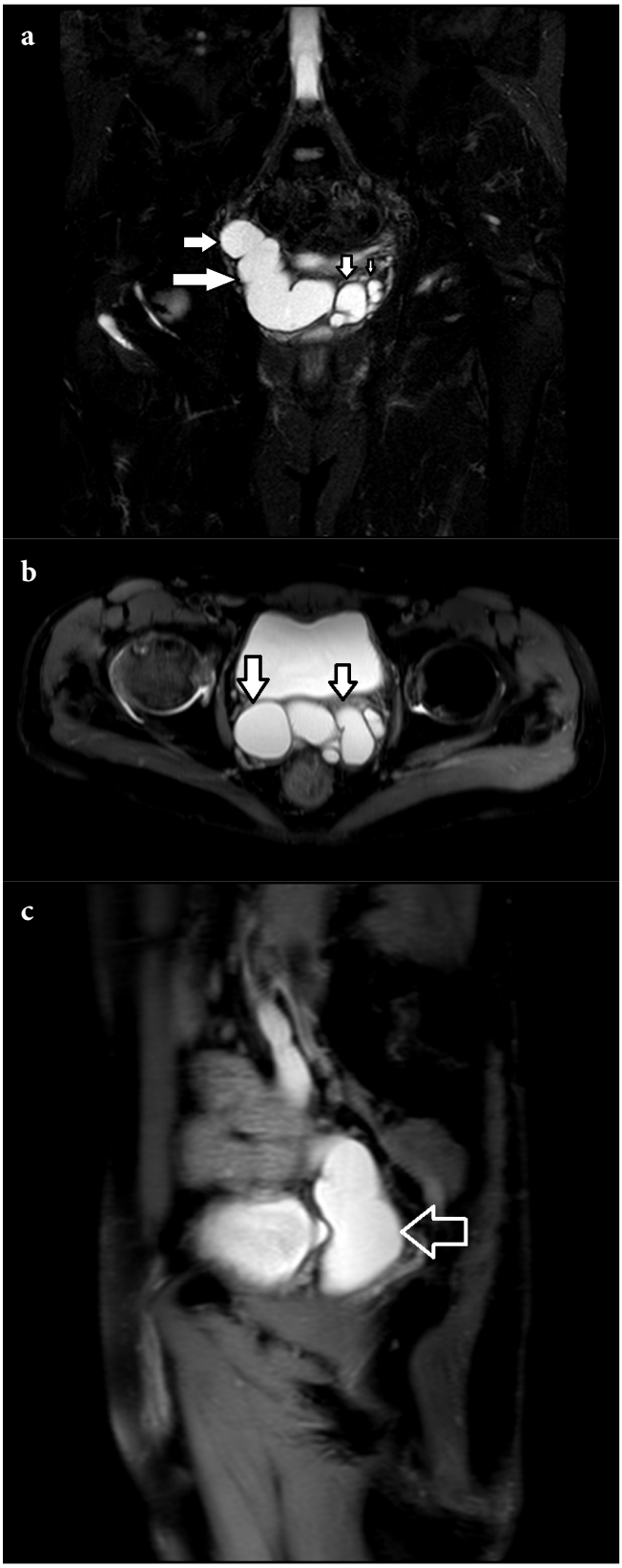

Fig. 5. On T2-weighted fat-sat coronal **(a)** and axial **(b)** images; Tubular enlargement was detected in the cystic structure starting from the bilateral prostate central to the lateral and extending from the bladder inferior to the right.

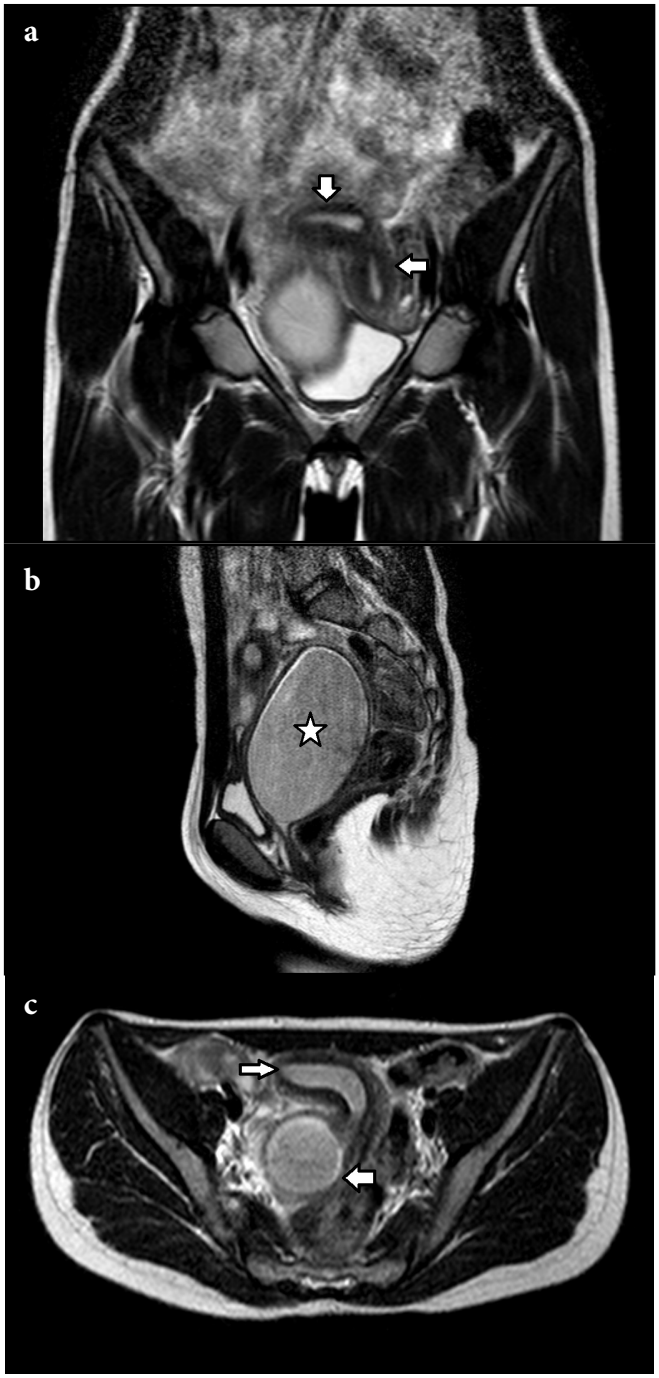

Fig. 6. On MRI coronal T2-weighted image **(a)**, an endometrial cavity showing two separate endometrial bands (uterine didelphys) surrounded by separate muscle layers was observed. And to the right of this, there is an obstructed blind hemivagina. Sagittal T2-weighted image **(b)** showing dilation of cervical canal with abrupt termination at vaginal fornix , resulting in obstructed hemivagina. Endometrial cavity was dilated and contained hemorrhagic collection. Axial T2-weighted image **(c)** showing two separate uterine horns and distention of endometrial cavity.

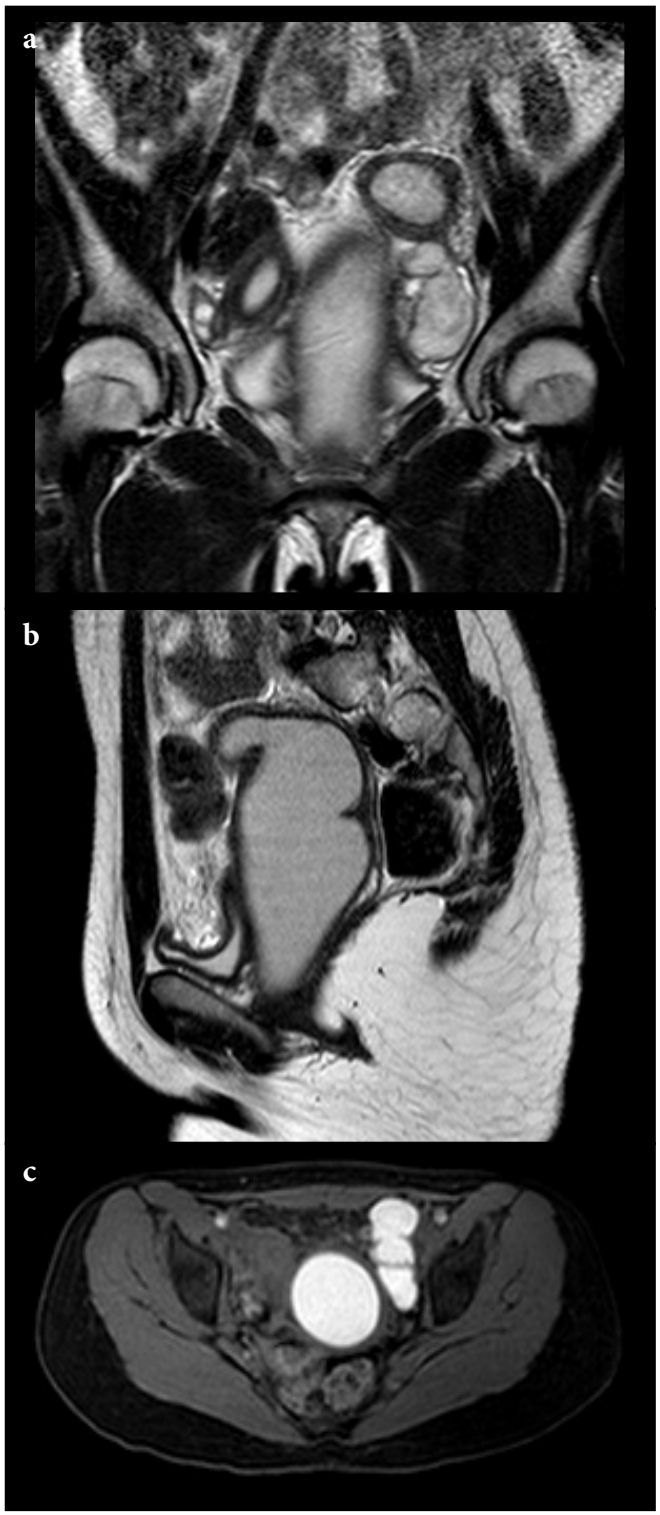

Fig. 7. In T2-weighted coronal MRI; Two separate endometrial cavities (a), enlargement of the cervical canal (arrow) with sudden termination of the vaginal fornix in the sagittal image (arrow), hemorrhagic collection in the endometrial cavity with obstructed hemivagina **(b).** In the axial fat-sat image; hematosalpinx image is observed in the left tuba (long arrow) **(c).**

resulted in obstructed hemivagina, which showed the cervical canal dilation with a sudden termination in the vaginal fornix. The endometrial cavity was dilated and contained a hemorrhagic collection. (**Fig. 6.b**). In T2-weighted axial images; Distention of two separate uterine horns and right endometrial cavities was detected (**Fig. 6.c**). The findings were consistent with Herlyn-Werner-Wunderlich syndrome.

Case-5. 19 years-old female patient with previously diagnosed renal agenesis admitted with irregular and painful menstruation, infertility, recurrent cyclic abdominal pain and mass complaints in the pelvic region. On physical examination; there was a palpable, well-defined soft abdominal mass extending towards the superior in the pelvic area. On gynecological examination, imperforated hymen and very enlarged, bulging uterus-cervix were detected. In the MRI examination; there was two separate endometrial cavities, widening of the cervical canal with sudden termination in the vaginal fornix, hemorrhagic collection in the endometrial cavity with obstructed hemivagina on coronal T2 **(Fig. 7.a)**, sagittal **(Fig. 7.b)** and axial T1 weighted images **(Fig. 7.c)**. There was also a hematosalpinx image in the left tuba. Radiological and clinical findings confirmed the diagnosis of Herlyn-Werner-Wunderlich syndrome.

DISCUSSION

Zinner syndrome is a Wolffian duct abnormality known with unilateral renal agenesis, ipsilateral seminal vesicle cyst and ejaculatory duct obstruction. HWWS is a rare mesonephric duct malformation with mullerian duct anomaly characterized by uterus didelphys, clogged blind hemi-vagina and ipsilateral renal agenesis (OHVIRA) syndrome. It was first reported by Wilson in 1925 (4).

Congenital anomalies of kidney and urinary tract are birth defects that affecting approximately 1% of live births (5). These anomalies include a wide range of malformations such as obstruction of ureteropelvic junction, kidney dysplasia, hydropic or ectopic and short ureters caused by deficiencies in embryonic kidney and lower urinary tract development. Although many gene sequences have been identified, the genetic causes of these malformations are still largely unknown (6). The morphogenesis of the urogenital system is affected by the nephric duct (ND), a common structure also known as the Wolffian duct (7). It is said by the authors that 1-2% of the cause of infertility in men has ND defects (8). Malformations that show a common etiology between the development of the urinary and genital system in the kidneys of patients with hymen impereforation of newborn girls are observed.

Zinner syndrome is based on the common origin of ureter buds and seminal vesicles from the Wolffian duct, associated with upper urinary tract abnormalities and seminal vesicle malformation (9). This syndrome occurs after an inadequate movement in the first trimester of embryogenesis. The ureteral bud originates from the dorsal aspect of the distal mesonephric canal and extends dorsocranially to meet and stimulate the transformation of the metanephric blastema to form the adult kidney. The mesonephric duct is divided into epididymis, paradidim, vas deferens, ejaculatory duct, seminal vesicle and hemitrigon under the influence of testosterone and anti-muller hormone (10). Alternatively, there will be abnormal ureteral budding, which leads to ipsilateral kidney agenesis or dysplasia and atresia of the ejaculatory duct and, consequently, to occlusion and cystic dilatation of the mesonephric duct (11).

HWWS is an anomaly it's etiopathogenesis is not clearly explained and its true incidence is unknown. Development in embryological period is affected by genetic and environmental factors. HWWS also moves towards the paramesonephric system and methanephrosis (12).

The upper two-thirds of the uterus, fallopian tube, cervix, and vagina develop from paired paramesonephric ducts. Then, caudally, it laterally passes into the mesonephric duct, and finally, in the midline, it comes in close contact with the paramesonephric canal from the opposite side and merges to form the upper part of the uterus, cervix and vagina (13). If they do not fuse, two separate hemiuterins and hemicervices occur, resulting in mullerian anomalies associated with OHVIRA syndrome (14).

As in our cases; most patients are asymptomatic from two to four decades until high sexual and reproductive activity periods (15). The clinical picture is related to the size of the seminal vesicle cysts. Cysts smaller than 5 cm are usually diagnosed on abdominal or digital rectal examination. Symptoms occur after progressive dilatation of the seminal vesicles due to the accumulation of secretions after inadequate drainage secondary to the ejaculatory canal atresia (16). In our cases, complicated appearance was observed with hemorrhage due to these drainage disorders. Seminal vesicles are localized in the posterior of the bladder and therefore enlarged cysts may cause different symptoms

due to bladder irritation, such as dysuria, recurrent urinary tract infections, infertility painful ejaculation epididymitis and prostatitis (17-18). Larger cysts (> 12cm) can cause bladder outlet obstruction, colon obstruction, or perianal pain.

Various imaging techniques can be used in the diagnostic study of these congenital malformations. These can be listed as intravenous urography, transrectal, ultrasonography, CT examination, cystoscopy and MRI. Intravenous urography can be used to assess collecting duct system abnormalities or absence and therefore may indicate kidney agenesis. Transrectal USG can be used to determine the size and location of the associated cystic mass and its association with the seminal vesicle or prostate. It may include symptoms suggestive of bleeding or infection but is limited to small field of vision. Pelvic USG can help in the differential diagnosis, to examine whether the kidneys are in normal location, and to accurately identify the relationship of the cystic mass in the pelvic area with adjacent structures.

CT examination can accurately demonstrate pelvic anatomy and atypical kidney structures, the presence of kidney or its association with associated pathology. MR imaging may be preferred due to its relatively better contrast resolution, seminal vesicles, pelvic structures, and collector system imaging. In both of our cases, MRI was performed following CT examination.

Treatment of Zinner syndrome; Surgical resection can be performed for symptomatic seminal vesicle cysts. Also, there is infertility and there is a desire for fertility, testicular sperm extraction can be performed. There are other methods such as transrectal or transurethral interventional procedures or transurethral resection of the seminal coliculus and vas deferens. In HWWS, a therapeutic laparoscopic evaluation or vaginal septum excision can be performed to remove obstruction.

As a result; Zinner syndrome and HWWS are congenital genitourinary anomalies accompanied by ipsilateral renal agenesis. The diagnosis of these patients, which can cause symptoms such as infertility, pelvic pain, and bladder irritation, can be selected as digital rectal examination, transrectal and abdominal USG, CT examination, and the more ideal imaging method MRI. Clinical suspicion and early diagnosis can contribute to directing treatment.

Compliance with ethical standards: This article does not contain any studies with human participants or animals performed by any of the authors.

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Conflict of interest: The authors declare that they have no conflict of interest.

Consent of informed: Written informed consent was obtained from the patients for publication of these reports and accompanying images.

Authors' contributions: ST, CG and MD analyzed and interpreted the patient data regarding the clinical and radiological findings of the patient. ST was major contributor in writing the manuscript. All authors read and approved the final manuscript.

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THE
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AIM

The New Journal of Urology (New J Urol) is a scientific, referred, open access publication of the Eurasian Uro-oncological Association. The society is a non-profit organization and it aims to increase the standards in the field of urology including education of the academicians, professionals and public. The New Journal of Urology aims to create or make contributions for the development of technical, scientific and social facilities and it also cooperates with any and all related institutions, organizations, foundations and societies from the national and international area for this purpose.

The journal' s financial expenses are covered by the Eurasian Uro-oncological Association. The journal is published quarterly – three times a year- in February, June and October, respectively and the language of the journal are English and Turkish.

The purpose of the New Journal of Urology is to contribute to the literature by publishing urological manuscripts such as scientific articles, reviews, letters to the editor, case reports, reports of surgical techniques, surgical history, ethics, surgical education and articles of forensic medicine.

The target group of the journal consists of academicians working in the field of urology, urologists, residents of urology and all other fields of expertise and practitioners interested in urology.

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