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1.1 Title page: It is the first page of the manuscript and prepared separately as MS Word document. It must include full names of the authors; highest academic degrees and the title of the article not exceeding 50 characters. Affiliations of the authors, departments and city names must be stated in order. Studies conducted in more than one centre must be marked with symbols. Full name, postal and e-mail addresses, phone and fax numbers of the author responsible for correspondence and corrections must be stated at the bottom of this page. It must be also explained if the study was previously presented in a scientific congress in accordance with aforementioned terms or if the abstract was published.

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Example: Müller C, Büttner HJ, Petersen J, Roskomun H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. Circulation 2000; 101: 590-3.

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Section in a book: Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, editors. Cardiovascular Medicine. 2nd ed. St Louis: Mosby; 1974. p.273-85.

Book with single author: Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Marcel Dekker; 1993.

Editor(s) as author: Norman IJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

Article presented at a meeting: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. P. 1561-5.

Scientific or technical report: Smith P. Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: 1994 Oct. Report No: HHSIGOE 169200860.

Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (dissertation). St. Louis (MO): Washington Univ. 1995.

Manuscript in electronic format

Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.

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Contents

Review

Original Investigations

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Contents

Case Reports

Index

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J Acad Res Med 2020;10(3):208-13

Urethral Stenosis and Urethroplasty in Male Elderly

Ali Ayyıldız

Adıyaman University Faculty of Medicine, Department of Urology, Adıyaman, Turkey

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ABSTRACT

Old age is defined as age 65 and older according to the World Health Organization. Urethral stenosis is a group of diseases with high morbidity in male society. Patients undergo surgery many times. In the elderly population, urethral stenosis develops especially secondary to diseases caused by aging. Stenosis occurs due to reasons such as benign prostatic enlargement, endoscopic urological manuplations, pelvic radiation therapy for rectal or prostate cancer, insertion of a probe. It is believed that reactions that develop at the cellular level due to hypogonadism in the elderly and the disadvantages caused by comorbidity, nutritional problems affect the course of urethral stenosis and the results of urethroplasty. Wound-related problems occur more often in the elderly. Researchers who share their urethroplasty experience with us express that all urethroplasty methods applied in young people can also be applied in the elderly population. But all interventions that will be made in the elderly population must be decided and implemented in detail. In this review, urethral stenosis, etiology, wound, elderly urethra, hypogonadism and their treatment were reviewed in the elderly. The number of published articles associated with elderly urethroplasty is quite small. There is a need for well-designed specialized research involving this age group.

Keywords: Male elderly, urethral stenosis, urethroplasty, hypogonadism, wound healing

INTRODUCTION

Unfortunately, there are several published articles when we look at the stenosis and treatments of the urethra involving the elderly population. Studies involving urethroplasty and its consequences in older people are almost non-existent. In most cases, the article on urethral stenosis and its treatments contains information about all age groups and the results of the study. In this review, an overview of old age, etiology, treatment methods and results, elderly wound and wound healing were reviewed in elderly patients with urethroplasty due to urethral stenosis. Isolated studies of urethral stenosis and urethroplasty are needed in the group of 65 years and older.

Elderly

According to the World Health Organization, age 65 and older is considered chronologically elderly. Old age is a natural and inevitable period of life, such as childhood, youth, adulthood, in which the interaction between genetic structure and the environment is observed at the highest level, physiological and spiritual changes occur, with complex aspects, seen in all living things (1). Even if each person is chronologically the same age, their physiology, biochemical and genetic structure are different, so they also react differently to diseases and treatments.

Overview

Chronological, biological and physiological ages should be considered while evaluating urethral injury and treatment in old age. Note the difference between chronological and biological aging. Accordingly, it has been stated that different organs and tissues in a person's body may have different biological aging rates compared to that person's chronological age, as well as different

ORCID ID of the author: A.A. 0000-0003-3724-2516.

Corresponding Author: Ali Ayyıldız,
E-mail: urology52@gmail.com

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J Acad Res Med 2020;10(3):208-13

individuals of the same chronological age may have very different biological aging rates. We act according to chronological age in our studies and statistical evaluations. Although they have the same chronological age, it should be assumed that the biological and physiological characters are different, which will have a positive or negative impact on wound healing.

Biological aging is the structural and functional change of the body during the development process. Our general way of life has an effect on the aging of our cells. With aging, continuous and inevitable decreases in productivity and physiological processes are observed. This is called physiological aging. Body composition, cardiovascular system, kidneys, digestive system, liver, brain, nervous system, lungs and functional deficiencies occur in the endocrine system (1).

Mortality in old age has decreased in some countries, and according to data from more than 30 developed countries, the probability of survival between the ages of 80-90 is about 37% on average. In some countries, the probability of survival exceeds 50% at the age of 80-90 (2).

Urethral stenosis disease is common and costly, observed in 0.6% of men and is stated to have created an economic cost of over $200 million in the United States in 2000. Advances in technology have increased endoscopic surgeries, and the associated risk of developing urethral stenosis has also increased. The epidemiology of stenosis disease is well defined, but the underlying basic pathophysiological mechanisms are still not well understood (3). Liu et al. (4), in the urethral stenosis series of 262 patients, reported the proportion of older people over 65 years of age as 24.8%. One in every four patients appears to be elderly (4).

Aged Urethra

Testosterone is important in the development of the urethra, for the integrity and function of the smooth muscles of the corpora cavernosa. Due to a decrease in testosterone levels in old age, there is a decrease in androgen receptors and periurethral vascularity in the urethra (5). A study identified a significant increase in urethral atrophy risk and artifical sphincter erosion due to a decrease in serum testosterone (6). For this reason, it has been suggested that there may be an increase in urethral stenosis and an inability to achieve treatment results due to a decrease in androgen, which develops secondary in the elderly (3).

Aging and wound healing play an important role in the micro-level structure of the urethra, and extracellular matrixes are necessary in the healing and proliferation process, as in all tissues (7). Matrix metalloprotein enzymes (MMP) increase with aging (8). It has been stated that even the urethral plaques of hypospadias in childhood show significant age-related structural changes, and these changes may play a role in urethral healing after hypospadias repair (9). The MMP enzyme family plays a key role in embryonic development, organ morphogenesis, ovulation, embryo implantation, wound healing, angiogenesis and apoptosis (8). Extracellular matrix and MMPs affect all tissues and reactions in old age. Experimental studies on this subject are continuing in urethral strictures (10).

Etiology and Stenosis Localization

Some of the most common etiologies of stenoses are lichen sclerosis, trauma, iatrogenic and infections (11,12). Sexually transmitted diseases, which are common in past times, today cause less urethral stenosis after new medical treatments. For this reason, the etiology of urethral stenosis also changed in old age (13). Pelvic radiation therapy is also a factor due to cancer treatments in old age (3). Urethral stenosis of iatrogenic or idiopathic origin are most common in industrialized countries (14). Currently, the most common cause of panurethral stenosis is genital lichen sclerosis (15). When all stenosis are evaluated, iatrogenic causes constitute almost half of the cases (13). Stenoses are most often seen in elderly patients secondary to urological instrumentation (3). Because a large number of translansurethral resections are performed due to prostate diseases and bladder tumors (16-18). Santucci et al. (17) stated that etiological factors developed due to 43% iatrogenic, 14% trauma, 14% prolonged catheter duration, 9% radiation therapy, 7% infection, 7% previous urethroplasty, and 3% radical prostatectomy, respectively, in their series of 70 patients over the age of 65. Schwetner et al. (13) identified the cause of stenoses as 26% iatrogenic, 9.5 % trauma, 45% instrumentation, 12% catheter, and 7% infection in their study involving 32 patients in the same age group. As it is seen, stenoses that develop secondary to endoscopic prostate and bladder operations in old age take the first place. Although it was previously known that the success rates of endoscopic treatment with internal urethrotomia were poor, it was considered the first option in practice, as limited life expectancy was considered in elderly patients (19). Although life expectancy has increased, when we look at population-based studies, most clinicians still use internal urethrotomia as the first option in our country for various reasons, although it varies from country to country (2,17,20). However, open urethroplasty has the best results (13,15,17,21-25).

Looking at the location of the stenosis, bulbar region is observed in the first place in the elderly (13,18). Spencer et al. (3), in their study investigating the relationship between hypogonadism and urethral stenosis, defined the most common place of stenosis in the two different groups as 53% and 57% at the bulbomembranous level. However, these groups include not only the elderly but also those under 65 (3). Schwentner et al. (13) confirmed that the bulbar region took the first place in terms of stenosis localization, similar to other researchers, in their series of 42 patients, but unlike other authors, they explained a high rate of 64%.

Comorbidity

As we know, comorbid diseases increase in old age (26). Therefore, considering the co-diseases associated with urethral stenosis, it is observed that diabetes, obesity and hypertension are most common, respectively, while in cases of comorbidity, the failure of urethroplasty increases. Age progression increases

the likelihood of strictures. The occurrence of stenosis and risk of treatment failure are associated with obesity (27,28). It is not known exactly how co-observation of comorbid diseases with old age contributes to urethral stenosis, surgery and recovery or failure of treatment. Advanced studies are needed on this issue. In general, comorbid diseases leave damage at the level of tissues and cells. It is possible that the presence of cellular or tissue damage secondary to the urethra due to these comorbidities will affect the post-urethral surgery.

Testosterone and Hypogonadism

Age, diabetes and obesity are associated with hypoandrogenism (HA) (3,28). Testosterone is important in urethral development and cavernosal smooth integrity and function (29). HA involves a decrease in urethral androgen-related receptors and periurethral vascularity (5). Also, low serum testosterone levels increase the risk of urethral atrophy and artificial sphincter erosion (6). It is not unreasonable to assume this link, but it is still difficult to establish a clear link between HA and urethral stricture and treatment failure.

Testosterone has multiple actions in the body, such as sexual differentiation and its effects on reproduction, muscle, bone, hematopoiesis, and behavior (30). Measurement of testosterone has been included in biochemical uncertainty assessments (31). As we know, testosterone is already declining in aging men, and it remains unclear at what point this decline is clinically significant. There are different attempts in relation to the topic to describe the status of low testosterone in aging men (3,30). It is not known exactly how testosterone or other androgenic receptors play a role in both urethra healing and other tissue and organ healing. Low testosterone due to secondary hypogonadism is due to insufficient gonadotropins, as most seniors have developed testicular failure. A study by Corona and Maggi (32) revealed concomitant metabolic diseases in about 90% of men with secondary hypogonadism. These diseases have been observed in more than 70% of men. All systems are affected in old age.

Androgen-dependent processes include not only the urethra, but also spongious tissue, and the vascular environment in spongious tissue. In case of androgen deficiency, the development of degeneration, atrophy and fibrosis in vascular and spongious tissue will contribute to the physiology of urethral stenosis. Moreover, in the case of hypogonadism, there is an increase in the level of systemically circulating proinflammatory cytokines (3). Suppression of systemic inflammatory responses was found when testosterone was administered externally to patients with hypogonadism (33,34).

Treatments

Before planning treatment, the urethra must be fully evaluated. For this purpose, retrograde urethrography, combined cystouretrography, urethroscopy should be performed first. Alpha blockers, which are started a few days before combined cystouretrography or 5-6 hours in advance, will increase the opening of the bladder neck, so an optimal image can be achieved. Endoscopy should then be planned both antegrad and retrograde depending on the condition of the stenosis.

In general, non-invasive techniques such as urethral dilation were abused in the past, and then internal urethrotomyr was presented as a definitive solution to the problem and became common without dilation and dilation. It was the first choice of doctors and patients, especially in short strictures. However, the problems and failure increased (20). Endoscopic treatment methods, which were widely used in the treatment of stenosis in the past, should be reviewed in terms of optimum treatment, since their success rates are low and they are not effective in long stenoses. Follow-up results of internal urethrotomy are poor (17). Nowadays, internal urethrotomy is recommended twice, only in appropriate cases (16,20).

A decrease in mortality in the elderly population today and a long life span have emerged as an unprecedented and unexpected situation. Therefore, the concept of urethral stenosis treatment had to be reconsidered in this population. From this point of view, it was reported that open urethroplasty should be raised as a first and valuable option in advanced older people over the age of 75 (35,36). Nowadays, the effectiveness of urethroplasty with a low complication rate has been proven with good surgical practices (37,38). Internal urethrotomy or dilatation are unacceptable procedures with failure rates of 50% in the first application and 100% in the second (17,20). Despite the aging population, especially in western countries, very few articles have been published about which open procedures can be applied in stenosis treatments (13,17). Santucci et al. (17) first published a study in 2004 in which they showed open urethroplasty results, complication and failure rates in the elderly group. This was the first article we could find in PubMed's scan. After a long time, in 2010, Schwentner et al. (13) shared the results of onlay skin graft, in which they performed open urethroplasty in elderly patients. According to our information, no further studies have been published on PubMed until 2020.

A gold standard treatment method, which we can say that the following technique is suitable for strictures, has not been defined yet. However, a tension-free anastomosis, spongiofibrosis, and the length of the stenosis are effective in determining the open urethroplasty method (35-38). Although buccal mucosa graft applications are most popular in young patients, there are concerns that oral factors such as poor oral hygiene, leukoplakia and dental prosthesis will disrupt the quality of the graft in older patients (13,39,40). Submucosal fibrosis may occur in those with long-term tobacco use and grafts taken due to poor oral hygiene (41-43). In panuretroplasties, although complication rates are minimal even when oral mucosa grafts are used, this rate is 17.5%. In this study, Schwentner et al. (13) showed that dorsay onlay techniques are effective and reliable in older people. There are no very detailed studies on the results of graft intake in the elderly (14). The only treatment option for long stenoses or panurethral stenoses is the application of urethroplasty using alternative methods of operation. Considering etiological factors, the characteristics of

J Acad Res Med 2020;10(3):208-13

stenosis, previous operations, the degree of fibrosis, the presence of tissues to be used as flaps or grafts, surgical experience and preference are effective factors in decision-making (16).

Many single or double-stage surgical techniques have been used in the treatment of long and other strictures. While Orandi penile skin, Quartey preputial skin flap, McAninch fasciocutaneous penile circular flap were used as flap; Techniques such as dorsal oral mucosa with Asopa ventral urethrotomy, Johanson procedure, oral mucosa grafts are used as graft. Recently, thanks to Kulkarni and other techniques, single-stage procedures using grafts and flaps have become popular, with comparable success rates, especially in the treatment of stenoses due to previous urethroplasties and radiotherapy (15,16,20,35,44-49). Bulbar urethral stenosis is treated using either direct (end-to-end anastomosis) or anastomosis techniques with free dorsal graft over the corporacaavernosa, or using epilated biaxial scrotal skin flap or free preputial skin or buccal mucosa, or with grafts placed ventrally or dorsally placed. Recently, the use of the buccal mucosa has increased in proximal urethral stenosis, which includes the membranous area. If the length of the stenosis is over 6 cm, two-stage urethroplasty is a good option (48-52). According to the preference and experience of the surgeon, applications other than the techniques described above can also be performed. However, although urethroplasty is considered the gold standard treatment, relapse rates still appear to be between 8.3 and 18.7% (53). Mundy (54). Published their results of patch urethroplasty for posterior urethral strictures over the age of 55. In their study, they stated that age factor did not play a role in failure, instead, retrograde spongiosal blood supply decreased in the elderly, ischemia occurred, and antegrade urethral blood supply was impaired especially in posterior urethral separation injuries (54).

In general, as the length of age and stenosis increases, the failure of urethroplasty increases. It is theoretically believed that when graft or flap is used in urethroplasty in the elderly, success rates will decrease, complications will increase, especially due to the presence of comorbidities (36,55). Although microvascular insufficiency in the elderly with diabetes, peripheral vascular disease and neuropraxia to be caused by potential ischemic extremity, which may develop due to excessive lithotomy position during the operation, and post-operative pulmonary edema that may develop due to cardiac and renal failure, studies have shown us the contrary (37,55,56). It is stated that problematic patients can be evaluated in coordination with anesthesiologists before the operation and operations can be performed (14). The use of oral mucosa may not be appropriate because of the increase in oral diseases as the age progresses, oral leukoplakia and head and neck tumors, and radiotherapy (39-43). However, since the side effects such as pain, swelling, and numbness are minimal, the success of urethroplasty will increase if the selection is still buccal mucosa in suitable cases (13,15,57). Because it has a higher capacity of elasticity and mechanical stability than skin grafts (14,58). Pedicle flap urethroplasties are not recommended in elderly patients due to their higher rate of unsuccessful results. Barbagli et al. (49) found that both skin and buccal mucosa grafts were more successful than flap procedures (26). Posteriorly applied grafts can make urethroplasty suitable in elderly patients, with the advantage of being fed with the abundant blood inherent in the corpora cavernosa (14,26). In addition, mechanical support of cavernosal tissue and dorsal onlay graft urethroplasty have been shown to provide long-term durability (59,60). Persistent perineal urethrostomy may be an option in complex cases with severe strictures, where urethroplasty has failed several times. Santucci et al. (17) applied this method in 4 of 70 patients (20).

Ventral interventions in accordance with the omega structure of the external sphincter are an appropriate approach to reduce incontinence in posterior urethral strictures. Despite this, the patient should be informed about dorsal interventions. Tissue engineering has also been applied in some centers recently. Urethra tissue produced in laboratories is used in surgeries (61). However, the researchers state that the tissue-engineered urethral tissue is very thin and requires careful surgery because of the high risk of tearing during surgery.

The Turkish Society of Urology and the Turkish Academy of Urology have published guidelines for diagnosis, treatment and follow-up protocols in urethral strictures. In this guide, the diagnosis, pathophysiology, treatment methods and follow-up protocols of urethral stenosis are summarized under the guidance of the American Urological Association and the European Urological Association guidelines. It is possible to find methods that can also be applied to older patients in the same manual and apply them in surgery, especially with more pictures and protocols to give them the opportunity to quickly browse in daily practice (62).

Elderly Wound and Healing

A wound can occur spontaneously, as well as iatrogenically, including operations. Surgeons accelerate the healing of surgical wounds thanks to the methods they have developed. However, factors such as patients' physical condition, tissue and immune systems, nutritional status and comorbidity due to their chronological, biological, physiological aging are effective in wound healing. In an epidemiological study that lasted 5 years with chronic wounds and examined 1158 wounds, it was reported that the wound closure time was significantly slower in older patients than in younger patients, and the wound closure time slowed after the age of 60 (63).

In wound healing; There are hemostasis, inflammation, proliferation and maturation phases. All of these phases are affected in the elderly. With increasing age, the number of platelets adhering to the injured endothelium and the release of growth factors increase (64). In elderly individuals, the components involved in inflammation reach the wound later, and therefore the inflammatory response is delayed. In addition, capillary permeability at the injury site decreases, so there is a slowdown in the transition of leukocytes to the wound site. In experiments with older animals, it was found that the number of phagocytic macrophages and the phagocytic skills of macrophages and the production of

growth factors secreted by macrophages decreased with age (65). The response to hypoxia in the elderly is also impaired. With increased age, there is a decrease in proliferative responses of keratinocytes, fibroblasts and vascular endothelial cells. There are also regressions in collagen synthesis and angiogenesis process. All these negatives can lead to delays in healing the wound and failure to close the wound (66). With age, the strength of the tissue to resist tears decreases, and this is explained by the decreasing collagen fibers. In elderly individuals, the strength of the wound is gained in a longer time than the young people and the strength of the wound obtained is weaker than the young individuals. Common comorbid diseases facilitate wound formation and make wound healing difficult. Factors such as reduced levels of hormones, nutritional problems, stress, obesity and multiple drug use also negatively affect wound healing. Among the factors affecting wound healing in the elderly; nutritional problems that may accompany chronic diseases, dermis thickness of the skin, protection and immune response against microorganisms, serum albumin level, collagen production, pressure and feel sensations, loss of tissue elasticity, decrease in partial oxygen pressures due to respiratory problems and tissue oxygen deficiency (64-67).

CONCLUSION

Although comorbid diseases increase in old age, mostly diabetes and cardiovascular diseases, nutritional disorders, decrease in androgen amount and hypogonadism, development of urethral atrophy, delays in wound healing, the results of urethral stricture treatment and urethroplasty application are satisfactory. Life expectancy has increased in most countries nowadays. For this reason, open urethroplasties should replace optical internal urethrotomy, which has been introduced as a treatment option with low success rates. There is no data except for a few published articles on this subject. There is a need for projects and scientific studies targeting the elderly group in order to develop clearer and scientific attitudes.

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J Acad Res Med 2020;10(3):208-13

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Role of Red Cell Distribution Width in Evaluation of Inflammatory Bowel Disease Activity

Deniz Öğütmen Koç[1], Murat Keğin[2]

[1]University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Gastroenterology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey

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ABSTRACT

Objective: We aimed to determine whether red cell distribution width (RDW) is useful in evaluating the activity and remission periods of inflammatory bowel disease (IBD).

Methods: One hundred thirty-two IBD patients, consisting of 98 ulcerative colitis (UC) patients and 34 Crohn's patients, were included in this retrospective study. Serum C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), leukocyte and platelet counts and hemoglobin (Hb) concentrations were evaluated separately during disease activity and remission periods. Disease activity for UC and Crohn's disease was determined by Mayo score and Crohn's Disease Activity Index (CDAI), respectively.

Results: The median age (interquartile range) was 37.5 (29-50) and the duration of the disease was 29.4±44.3 months in the patients included in the study. RDW, ESR, CRP values, leukocyte and thrombocyte counts were significantly active periods compared to remission periods ($p<0.01$), while Hb concentration was significantly lower ($p<0.001$). ESR, CRP, and platelet levels were significantly associated with Mayo score in UC patients and CDAI severity in Crohn's patients ($p<0.05$). No association was observed between RDW and disease severity according to IBD activity scores. RDW, ESR, CRP values and platelet counts were significantly higher during the active periods of patients with UC (36.7%) and Crohn's disease (41.2%) with anemia than those without anemia ($p<0.01$).

Conclusion: RDW can be used as an indicator of activity and remission in IBD patients. RDW can be a useful additional marker as an easy and inexpensive tool to monitor disease activity, predict relapse, and follow-up treatment.

Keywords: Red blood cell distribution width, inflammatory bowel disease, activity, remission

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal system that occurs with periods of activity and remission throughout its clinical course (1). It contains 2 main phenotypes: Crohn's disease and ulcerative colitis (UC). UC is characterized by inflammation limited to the colon mucosa, while in Crohn's disease, transmural inflammation is observed, which can affect any part of the gastrointestinal tract (2). In IBD patients, the value of hemoglobin (Hb) concentration and platelet count and inflammation markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) were reported in disease activity assessment and treatment effectiveness monitoring (3,4). Recent studies have highlighted the possible role of red cell distribution width (RDW) as an additional inflammatory marker in IBD (5-7). RDW is a measure of the size variability and heterogeneity

ORCID IDs of the authors: D.Ö.K. 0000-0003-2738-625X; M.K. 0000-0002-0596-2386.

Corresponding Author: Deniz Öğütmen Koç,
E-mail: drdenizkoc@gmail.com

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(anisocytosis) of erythrocytes in peripheral blood. RDW, which is part of a whole blood count, is a blood parameter that is routinely measured, automatically reported. It is obtained by dividing the standard deviation of the erythrocyte volume distribution by the mean corpuscular volume (MCV) and multiplying by 100 (8). RDW is being used as an auxiliary index in the diagnosis of anemias caused by iron deficiency, B12 or folic acid deficiencies; this has led to it being considered as a potential screening marker for colon cancer and celiac disease (9-11).

Recently, RDW has been shown to have clinical significance for evaluating the clinical consequences and severity of various pathological conditions such as cardiovascular and respiratory diseases, sepsis, malignancies, renal dysfunction, autoimmune diseases, and (11,12) has been found to be a strong predictor of mortality in cardiovascular diseases (13). It has also been observed to be important in assessing mortality rates and survival in hospitalized patients and to be a prognostic biomarker in adults 45 years and older (12,14). Systemic factors that alter erythrocyte homeostasis, such as inflammation and oxidative stress, are thought to play a role in the mechanisms underlying RDW's association with survival (14). High oxidative stress can reduce the survival of erythrocytes, so that a higher-grade anisocytosis can be observed due to the increased proportion of immature erythrocytes in circulation (15). In addition, the relationship between the increase in systemic inflammation and anisocytosis supports the role of RDW as an important inflammatory marker (11).

In this study, we compared RDW values measured during the activity and remission periods of IBD patients. We aimed to determine whether RDW can be used as a marker in activity monitoring and recurrence prediction of IBD patients.

METHODS

A total of 132 patients IBD patients who were hospitalized or followed as outpatients were included in this study. Medical records of the patients were reviewed retrospectively. Malignancy, rheumatic diseases, acute infectious diseases, cardiovascular diseases and patients who did not continue the follow-up were excluded from the study. The study group consisted of 98 (74.2%) patients with UC and 34 (25.8%) patients with Crohn's disease. During periods of activity and remission, serum RDW, CRP, ESR values, leukocyte and platelet counts, Hb concentration, mean platelet volume (MPV), MCV, and iron (Fe) results were evaluated. Disease activity for UC and Crohn's disease was determined with Mayo score and Crohn's Disease Activity Index (CDAI), respectively. UC patients according to Mayo score: (1) remission <3; (2) 3≤ mild activity <6; (3) ≥6, moderate-severe activity. Crohn's patients according to CDAI: (1) remission <150; (2) 150≤ mild activity <220; (3) ≥220, moderate-to-severe activity. The presence of normal disease activity scores, tests, and clinical findings in patients was accepted as remission. Anemia was defined as Hb levels below 12 g/dL and 13 g/dL for female and male patients, respectively.

The analysis of the data was approved by the Ethics Committee of Taksim Training and Research Hospital, which verified that the study complies with the ethical rules of the Declaration of Helsinki (approval number: 36, date: 10.04.2019).

Statistical Analysis

The compatibility of numerical variables to normal distribution was tested with the Shaphiro-Wilk test. Student's t-test was used to compare normally distributed variables in two independent groups. The paired t-test was used to test the difference between two dependent measurements in normally distributed variables. Relationships between numerical variables were tested with Pearson correlation coefficient, and relationships between categorical variables were tested with chi-square test. SPSS Windows 22.0 package program was used in the analyzes. $P<0.05$ was considered significant.

RESULTS

Median age (interquartile range) was 37.5 (29-50) and disease duration was 29.4±44.3 months in 132 patients included in this retrospective observational study. Twenty (58.8%) of the Crohn's patients were male and 57 (58.2%) of the UC patients were male. The general characteristics of the patients are given in Table 1. Distribution according to disease location in UC patients is as follows: 23 (23.5%) patients proctitis, 41 (41.8%) left sided colitis and 34 (34.7%) patients pancolitis. In Crohn's patients, 19 (55.9%) patients had terminal ileitis and 15 (44.1%) patients had ileocolitis. There were no significant differences in age, gender, and duration of disease between UC and Crohn's patients ($p>0.05$). When patients were evaluated for anemia, 14 (41.2%) of Crohn's patients and 36 (36.7%) of UC patients had anemia, there was no significant difference in the presence of anemia between the two groups ($p>0.05$). In addition, there was no difference in RDW, ESR, CRP values, platelet count and Hb concentration during activity and remission periods between UC and Crohn's patients ($p>0.05$).

RDW values were significantly higher in active periods of IBD patients compared to remission periods ($p=0.007$). In addition, while ESR, CRP values, leukocyte and thrombocyte counts were significantly higher in IBD patients during their active periods when compared with their remission periods ($p<0.001$); Hb concentrations, MPV and Fe values were significantly lower in the active period ($p<0.001$). There was no significant difference in MCV values between the activity and remission periods ($p>0.05$). When UC and Crohn patient groups were evaluated separately; RDW, CRP, ESR values, leukocyte and platelet counts were found to be significantly higher in the activity period of both groups (Table 2).

According to the disease localization, there was no significant difference in RDW values between patients with proctitis, left-sided colitis, and pancolitis for UC diseases; and between patients with terminal ileitis and ileocolitis for Crohn's disease ($p>0.05$). CRP, ESR and leukocyte values were found to be higher in the

pancolitis group compared to the left-sided colitis and proctitis groups in the active period of UC (p=0.004, p=0.014, p=0.029, respectively). There was no significant difference in inflammatory markers between ileitis and ileocolitis patients in the active period of Crohn's (p>0.05). In our study, in terms of Hb concentrations in UC patients, a significant difference was found between the groups with mild, moderate and heavy activity in the Mayo score (p=0.003), but no difference was found between the mild and moderate-severe CDAI groups in Crohn's patients (p=0.105). ESR, CRP values and platelet counts increased significantly in parallel with Mayo score and CDAI severity, while no significant differences in RDW values were observed in both groups (p>0.05) (Table 3).

Table 1. General characteristics of patients with Ulcerative Colitis and Crohn's disease

	Ulcerative colitis (n=98)	Crohn (n=34)	p
Gender (M/F) (n)	57/41	20/14	0.556
Age, year	40.8±14.6	37.7±12.5	0.271
Duration of the disease, month	29.7±45.9	28.3±39.9	0.869
Localized disease, (n, %)			
- Proctitis	23(23.5)	-	-
- Left side colitis	41(41.8)	-	-
- Pancolitis	34(34.7)	-	-
- Terminal ileitis	-	19 (55.9)	-
- Ileocolitis	-	15 (44.1)	-
Anemia, (n, %)	36 (36.7)	14 (41.2)	0.397

n (%) was used for categorical variables and mean ± standard deviation was used for numerical variables.
M: male, F: Female

Table 2. Comparative analysis of inflammatory markers in IBD patients by activity and remission

	Ulcerative colitis (n=98)			Crohn (n=34)		
	Activity	Remission	p	Activity	Remission	p
Hb (g/dL)	12.9±1.9	13.6±1.7	<0.001*	12.9±2.2	13.6±1.8	0.009*
Htc (%)	39.3±5.1	40.7±4.5	0.003*	39.4±5.9	40.9±4.7	0.038*
WBC ($10^3/mm^3$)	8.3±2.7	7.0±1.9	<0.001*	8.4±2.1	7.3±1.7	0.002*
PLT ($10^3/mm^3$)	298.2±112.4	268.2±81.1	0.002*	336.0±115.7	278.0±67.4	0.002*
ESR (saat)	27.0±26.4	13.6±11.2	<0.001*	35.1±21.6	14.2±9.4	<0.001*
CRP (mg/dL)	19.1±37.8	4.2±8.3	<0.001*	37.4±50.0	5.1±4.2	0.001*
RDW (%)	15.3±3.0	14.6±2.1	0.050	16.0±3.5	14.9±2.0	0.047*

*p<0.05, mean ± standard deviation.
IBD: inflammatory bowel disease, Hb: hemoglobin, Htc: hematocrit, PLT: platelet, WBC: white blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: red cell distribution width

Table 3. Comparative analysis of inflammatory markers according to disease activity in IBD patients

	Ulcerative colitis (n=98)				Crohn (n=34)		
	Mayo score				CDAI		
	Mild (n=12)	Moderate (n=24)	Severe (n=62)	p	Mild (n=12)	Moderate-severe (n=22)	p
Hb (g/dL)	13.7±1.8	13.8±1.4	12.4±2.0	0.003*	13.8±2.1	12.4±2.1	0.105
WBC ($10^3/mm^3$)	6.9±1.3	7.7±2.6	8.7±2.8	0.051	8.3±1.8	8.5±2.3	0.652
PLT ($10^3/mm^3$)	252.9±54.7	253.8±80.7	324.2±123.4	0.010*	269.8±109.1	372.1±104.6	0.001*
ESR (hours)	8.0±2.7	15.9±15.1	35.3±28.6	<0.001*	22.1±13.9	42.2±22.0	0.005*
CRP (mg/dL)	3.9±1.1	4.3±1.7	27.8±45.4	0.010*	11.7±15.1	51.4±56.8	0.001*
RDW (%)	14.8±1.5	14.5±2.7	15.7±3.2	0.230	14.8±2.5	16.7±3.8	0.200

*p<0.05, mean ± standard deviation.
IBD: inflammatory bowel disease, CDAI: Crohn's Disease Activity Index, Hb: hemoglobin, WBC: white blood cells, PLT: platelet, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: red cell distribution width

J Acad Res Med 2020;10(3):214-9

While there was a positive correlation between the Mayo score and ESR, CRP values, platelet and leukocyte counts (r=0.59, r=0.57, r=0.37, all p<0.001; r=0.29, p=0.004, respectively), there was a negative correlation with Hb concentration (r=-0.42, p<0.001). Similarly, positive correlation between CDAI increase and ESR, CRP values and platelet numbers (r=0.67, r=0.72, both, p<0.001; r=0.56, p=0.001, respectively) and negative correlation with Hb concentration (r=-0.54, p=0.001) were found in Crohn's patients. The relationship between RDW and Mayo score and CDAI was not statistically significant. RDW values of those with anemia in the active period of UC and Crohn's patients were found to be significantly higher than those without anemia (p<0.001). In addition, those with anemia during the activity period had higher CRP, ESR values and thrombocyte counts compared to those without anemia (all, p<0.01) (Table 4).

During the active period of the patients, negative correlation between RDW and Hb, MCV and iron values (r=-0.45, r=-0.48, both p<0.001; r=-0.23, p<0.01, respectively); and positive correlation between platelet values (r=0.27, p<0.01) were present. Similarly, there was a negative correlation between RDW and Hb, MPV, iron values in the remission period (r= -0.36, p<0.001; r= -0.19,; r= -0.24, both p<0.01) and a positive correlation between platelet values (r=0.25, p<0.01).

DISCUSSION

In this study, we found that RDW, a simple morphological marker of erythrocyte size heterogeneity, was significantly higher during active periods of IBD patients than during periods of remission. As far as we know, this study is the first to compare RDW values in the active and remission periods of the same group of patients.

In IBD, there is still no single gold standard test for assessing the activity, severity and outcome of the disease. Instead, a combination of symptoms, clinical examination, laboratory examinations, radiology and endoscopy and histology are used to assess activity and predict the course of the disease (3). In recent studies, RDW has been investigated as a marker of inflammation in the evaluation of disease activity and treatment decisions in IBD (6,7,16).

RDW reflects the variability in the size of circulating erythrocytes and does not incur additional costs, as it is routinely measured by automated laboratory equipment used to perform complete blood counts (8). Recently, RDW value has been used in the diagnosis of anemias caused by iron deficiency, B12 or folic acid deficiencies (17,18). In addition, there is an increase in RDW in cases such as severe blood loss that causes immature cells to be released into the bloodstream, hemoglobinopathies that cause erythrocyte shape change, hemolytic anemia or hemolysis (12,13).

The mechanisms mediating the relationship between high RDW values and IBD activity are not exactly known. Chronic inflammatory condition, causing immature erythrocytes to enter the circulation, can contribute to ineffective erythropoiesis and lead to increased RDW (14,16).

In IBD, proinflammatory cytokines such as interleukin-1b (IL-1b), IL-6, IL-10, tumor necrosis factor alpha and interferon gamma are produced by peripheral blood monocytes and mononuclear cells of the intestinal lamina propria (19-21). These cytokines may contribute to the development of anemia by inducing erythropoietin resistance (22). Also during inflammatory processes, the biological half-life of erythrocytes is reduced as a result of oxidative stress and lipid peroxidation. This promotes erythrophagocytosis and reduces iron recirculation. These facts lead to the retention of iron in phagocytes and the development of functional iron deficiency, that is, although iron is present in the body, it is not present for erythropoiesis (23). At the same time, more inflammatory activity probably leads to greater blood loss, increased hepcidin release, and decreased iron absorption from the intestine (24). These factors cause immature red blood cells to be released into the peripheral circulation, leading to an increase in RDW and anisocytosis (13).

In our study, we showed that increased RDW levels are associated with disease activity in IBD. We found that RDW increased during the activity periods of IBD patients and returned to normal in the remission period. Cakal et al. (5) showed that a 14% cut value for RDW had a sensitivity of 0.86 and a specificity of 0.75 when detecting active UC, and a 14.1% RDW cut value for Crohn's disease had a sensitivity of 0.78 and a specificity of 0.63.

As expected in the results of our patients, inflammatory markers such as ESR, CRP values, leukocyte and platelet numbers were significantly higher during the IBD active period. ESR, CRP values and platelet counts were higher in the group with severe Mayo score in UC patients and in the group with moderate-severe CDAI in Crohn's patients. But no significant association was found between RDW and disease activity scores.

Table 4. Comparison of inflammatory markers in active IBD patients with anemia status

	IBD (n=132)		
	Anemia (n=50)	No anemia (n=82)	p
CRP (mg/dL)	41.9±59.6	12.8±18.9	0.001*
RDW (%)	16.9±3.8	14.6±2.2	<0.001*
ESR (hours)	42.7±31.3	21.0±16.1	<0.001*
PLT (10^3/mm^3)	371.0±135.2	269.5±77.6	<0.001*

*p<0.05, mean ± standard deviation.
IBD: inflammatory bowel disease, CRP: C-reactive protein, RDW: red cell distribution width, PLT: platelet, ESR: erythrocyte sedimentation rate

Clarke et al. (25) found that RDW levels were higher in Crohn's patients compared to UC patients (14.9% versus 14.3%) and they associated this result with malabsorption, which is an additional cause of anemia in Crohn's patients. According to the data of their study, they reported that RDW values may be a marker in the separation of UC and Crohn's (25). Another study determined the RDW cut value at 14.45 with 70% sensitivity and 56% specificity in the differentiation of Crohn's disease from UC (7). In our study, there were no significant differences in RDW and other inflammatory parameters between UC and Crohn's patients in the active period.

Among our active IBD patients, RDW, CRP, ESR values and platelet counts were significantly higher in patients with anemia (37.9%). The result of our data shows that anemia increases in parallel with the severity of the disease. Song et al. (6) showed that RDW correlates with disease activity in anemic and non-anemic IBD patients; They found that RDW was the best independent indicator for predicting disease activity in Crohn's patients without anemia (6). However, in other studies, RDW was an important determinant as an indicator of active UC, while it was stated that CRP was the most sensitive and specific parameter in the evaluation of active disease for Crohn's patients (5,26).

According to our data, ESR, CRP and RDW values were significantly higher during the activity period of UC and Crohn's disease than during the remission period; a strong correlation was found between the severity of disease activity and ESR and CRP in both groups, but no correlation was found between them and RDW values.

CONCLUSION

We found that RDW values were high during activity periods of IBD patients, and declined to normal values during remission periods. According to our results, RDW as a cheap tool can be a useful marker for activity monitoring, recurrence prediction, and treatment monitoring of IBD patients when evaluated together with other inflammation parameters.

Ethics Committee Approval: The analysis of the data has been approved by the Ethics Committee of Taksim Training and Research Hospital, which confirms that the study complies with the ethical rules of the Declaration of Helsinki (approval number: 36, date: 10.04.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Author Contributions: Design - D.Ö.K., M.K.; Data Collection and/or Processing - D.Ö.K., M.K.; Analysis and/or Interpretation - D.Ö.K.; Literature Search - D.Ö.K., M.K.; Writing Manuscript - D.Ö.K.

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Congenital Urinary System Anomalies: Prenatal Diagnosis/ Postnatal Outcome

Miraç Özalp[1], Hatice Sonay Yalçın Cömert[2], Ömer Demir[3], Hidayet Şal[3], Turhan Aran[1], Mehmet Armağan Osmanağaoğlu[1]

[1]Karadeniz Technical University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Perinatology, Trabzon, Turkey
[2]Karadeniz Technical University Faculty of Medicine, Department of Pediatric Surgery, Trabzon, Turkey
[3]Karadeniz Technical University Faculty of Medicine, Department of Obstetrics and Gynecology, Trabzon, Turkey

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ABSTRACT

Objective: To evaluate the relationship of fetal urinary system anomalies with aneuploidy and additional structural malformations, to compare the preliminary diagnoses made in the prenatal period with the results of the postnatal period.

Methods: Two hundred eighty-two cases diagnosed as fetal urinary system anomaly in our clinic between 2016-2019 were evaluated within the scope of the study. Age, gestational week, gravida, parity, fetal gender, type of anomaly, presence of additional anomaly, prenatal diagnosis method, fetal karyotype result, termination status and postnatal results were recorded.

Results: Hydronephrosis (HN) was in the first place among fetal urinary system anomalies. When congenital malformations accompanying urinary system anomalies were examined, central nervous system anomalies were the most common group with 26.4%. Urinary system anomalies, which are most frequently associated with additional anomalies; bilateral renal agenesis (50%), bilateral multicystic dysplastic kidney (50%) and extrofia vesica (50%). Considering the karyotype results, trisomy was observed in 26% of the cases, PKHD1 in 4% and triploidy in 2%. According to the karyotype result, when the group with normal karyotype and trisomy group was compared, the difference between the presence of additional anomalies (p=0.004), bilateral HN (p=0.012) and termination results (p=0.002) was found statistically significant. The rate of cases followed in pediatric surgery clinic/outpatient clinic in the postnatal period is 26% and 38.2% of these cases have undergone surgical intervention.

Conclusion: Appropriate diagnosis, follow-up and treatment of urinary system anomalies that have a broad clinical spectrum, with a multidisciplinary approach, are of great importance in both the prenatal period and the postnatal period.

Keywords: Hydronephrosis, karyotype, polycystic kidney, prenatal diagnosis, trisomy

INTRODUCTION

Congenital urinary system abnormalities include structural and functional malformations of the kidney, urethra, bladder and urethra. With the advanced technology ultrasonography devices used today, it has become possible to detect many of these anomalies in the prenatal period (1). Congenital abnormalities of the kidney and urinary system (CAKUT) account for about 20-30% of all abnormalities detected in the prenatal period (2). The total

ORCID IDs of the authors: M.Ö. 0000-0002-2255-1642; H.S.Y.C. 0000-0002-5281-4933; Ö.D. 0000-0003-4376-8733; H.Ş. 0000-0002-3586-6125; T.A. 0000-0001-9488-9776; M.A.O. 0000-0001-5115-5262.

Corresponding Author: Miraç Özalp,
E-mail: ozalpmirac@gmail.com

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rate of CAKUT in live or stillborn infants is about 0.3 to 1.6 per 1,000 births (3).

The fetal kidney develops from the mesoderm layer, and the process that begins on the 26th day of embryogenesis goes through the stages of pronephrosis, mesonephrosis, and methanephrosis. Metanephrosis is the last stage of kidney development. It consists of methanephric mesenchyme and ureter bud, and begins to function between 6th-10th weeks. Fetal urine production starts in the 9th week of embryogenesis. Metanephrosis migrates from its initial caudal position and settles in the pelvis opposite the sacral somites, reaching its permanent location in the lumbar region in the 8th week of embryogenesis. The bladder and urethra develop from the urogenital sinus (4). Fetal urinary system abnormalities can be caused by defects in genes encoding signaling and transcription factors or monogenic abnormalities (5,6). Although some malformations are seen together with syndromes accompanied by multiorgan anomalies, most of the cases are non-syndromic. In addition, environmental factors such as exposure to teratogens during prenatal period may cause CAKUT by disrupting kidney morphogenesis (7,8).

Urinary system anomalies not only affect the existing system, but may also affect other fetal functions. Some of these abnormalities can cause oligohydramniosa and, as a result, fetal pulmonary hypoplasia, facial deformities, and limb contractures. Most urinary system abnormalities are progressive. Functional recycling is possible with intrauterine or postnatal treatment methods (9,10). For this reason, prenatal diagnosis of urinary system anomalies; it plays an important role in determining the timing, place and mode of birth.

In our study, our aim was to determine the frequency of fetal urinary system anomalies, to determine their relationship with aneuploidy and additional structural malformations, and to compare prenatal diagnoses with postnatal period results.

METHODS

In this study, 282 cases of fetal urinary tract anomaly detected during fetal anomaly screening or routine obstetric ultrasound examination in Karadeniz Technical University Faculty of Medicine, Clinic of Perinatology between January 1, 2016 and June 31, 2019 were retrospectively evaluated. Age, week of pregnancy, gravida, parity, fetal sex, type of anomaly, presence of additional anomaly, prenatal diagnosis method, fetal karyotype result, termination status and postnatal results were recorded for all pregnant women with fetal urinary system anomaly. Urinary system anomalies were divided into subgroups such as renal agenesis, hydronephrosis (HN), multicystic dysplastic kidney (MCDK), polycystic kidney (PCK), ectopic kidney, duplication of collector system, megacistis and posterior urethral valve (PUV). The most widely accepted renal pelvic diameter (RPD) scoring system was used to define and grade fetal HN. Accordingly, the limit value for the anteroposterior diameter measurement of the renal pelvis in the transverse plane was determined as 4 mm until the 32nd gestational week, and 7 mm at 33 and more gestational weeks. Cases of HN that underwent spontaneous resolution were excluded from the study during their follow-up in the prenatal period. For the purpose of prenatal diagnosis, each family that will be karyotyped was given genetic counseling prior to the procedure. Chorionic villus sampling (CVS), amniocentesis (AC) or cordocentesis (CC) were applied to the cases for genetic diagnosis. Written and verbal information was given to the families about the method of karyotyping and possible complications, informed consents were obtained. Interventions were performed with ultrasonography. Fetuses with aneuploidy or structural malformation incompatible with life were evaluated in the council consisting of perinatology, pediatric surgery and medical genetics doctors, and families were offered the option of termination of pregnancy. Evaluation of the newborn in the postnatal period was performed by pediatric surgery doctors within the first 7 days after birth.

For the study, the necessary ethics committee permission was obtained with the decision of the Ethics Committee of Karadeniz Technical University Faculty of Medicine (decision number: 2019/28).

Statistical Analysis

In the study, SPSS 24 Version was used for recording and calculating statistical data. (IBM Corp., SPSS Statistics for Windows, Version 24.0. Armonk, NY.) The suitability of numerical variables for normal distribution was tested by the Kolmogorov-Smirnov test. Categorical variables were determined using frequency and percentage; numerical variables were determined using mean and standard deviation or median and minimum-maximum values. The relationship between two categorical variables was investigated by chi-square test. The arguments were compared with the Mann-Whitney U test. The study was conducted in a 95% confidence interval and $p<0.05$ value was considered statistically significant.

RESULTS

The study group consisted of 282 pregnant women with fetal urinary system anomaly. The mean age of the pregnant women included in the study was 30, and the mean week of gestation diagnosed with fetal urinary system anomaly was 23 weeks. Fetal sex was found to be 158 male (56%), 117 female (41.4%) and 7 unspecified (2.5%). Table 1 shows the demographic characteristics of the cases.

Among the abnormalities of the fetal urinary system, HN was the first. In 198 pregnant women (70.2%), fetal HN was observed, of

Table 1. Demographic data

Age	30±5.4
Gravida	3±0.6
Parity	1±0.3
Diagnosed pregnancy week	23.2±5.6
Fetal sex, F/M/U*, n (%)	117/158/7 (41.4%, 56%, 2.5%)

*F: female, M: male, U: undefined

J Acad Res Med 2020;10(3):220-6

which 112 (39.7%) were unilateral and 86 (30.5%) were bilateral. In other pregnant women, unilateral MCDK in 15 (5.3%), bilateral MCDK in 2 (0.7%), unilateral renal agenesis in 8 (2.8%), bilateral renal agenesis in 4 (1.4%), PCK in 5 (1.8%), ectopic kidney in 16 (5.7%), collecting system duplication in 14 (5%), megacystis in 15 (5.3%), extrophia vesica in 2 (0.7%) and 3 of them (1.1%) had PUV (Table 2). An ultrasound image of the fetus diagnosed with a PUV was presented in Figure 1. Central nervous system abnormalities in 14 (26.4%) cases, fetal cardiovascular system abnormalities in 13 (24.5%) cases, and gastrointestinal system abnormalities in 7 (13.2%) were the most common groups in the study of other abnormalities accompanying urinary system abnormalities (Table 2). In addition, urinary system abnormalities that were most commonly associated with additional abnormalities were bilateral renal agenesis (50%), bilateral MCDK (50%), and extrophia vesica (50%) (Table 2). In addition to other organ abnormalities, anhydramnios developed in 7 cases (13.2%).

A total of 50 cases (45.9%) of karyotyping were performed, including AC for 37 cases, chorionic villi biopsy for 8 cases and CC for 5 cases. Fifty-nine patients (54.1%) refused to undergo karyotyping, although it was recommended. Karyotype results were observed to be normal in 34 (68%) patients. In one case, triploidy (69XXX) and in two cases, the *PKHD1* gene was positive, making all the remaining aneuploidy trisomies, and trisomy was present in 13 (26%) patients (Table 3). An ultrasound image of the fetus with PKHD1 was shown in Video 1.

When the normal and trisomy groups were compared according to karyotype results, a statistically significant difference was found between the groups in terms of termination and bilateral HN (p=0.002, p=0.012) (Table 4). As a result of the karyotype, additional anomalies were observed, mainly 46.2% CNS anomaly and 23.1% CVS anomaly in trisomy patients. Two (15.4%) of cases

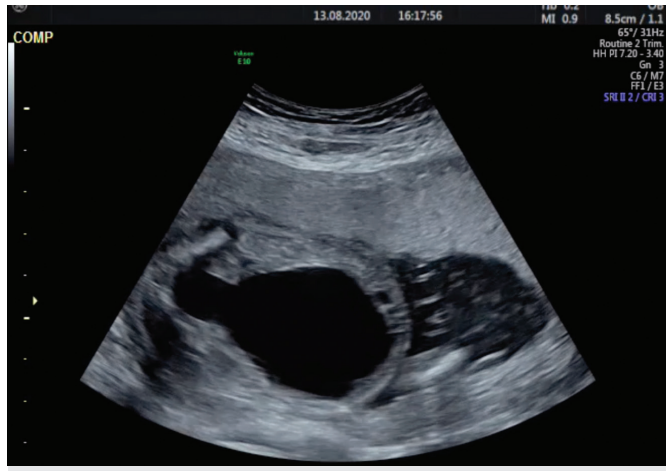

Figure 1. Ultrasound image of the fetus diagnosed with posterior urethral valve

Table 2. Distribution of fetal urinary system anomalies and accompanying anomalies

Urinary system anomalies	n	%	Additional anomaly (n)	Additional anomaly (%)
Unilateral hydronephrosis	112	39.7	23	20.5
Bilateral hydronephrosis	86	30.5	17	19.8
Unilateral MCDK	15	5.3	3	20
Bilateral MCDK	2	0.7	1	50
Unilateral renal agenesis	8	2.8	3	37.5
Bilateral renal agenesis	4	1.4	2	50
PKD	5	1.8	1	20
Ectopic kidney	16	5.7	-	-
Duplication of collector system	14	5	-	-
Megasistis	15	5.3	2	13.3
Extrophia vesica	2	0.7	1	50
Posterior urethral valve	3	1.1	-	-
	282	100	53	-
Accompanying anomalies	**n**		**%**	
CNS	14		26.4	
CVS	13		24.5	
GIS	7		13.2	
Face	5		9.5	
Skeletal dysplasia	5		9.5	
Single umbilical artery	9		16.9	
	53		100	

MCDK: multicystic dysplastic kidney, PKD: polycystic kidney disease, CNS: central nervous system, CVS: cardiovascular system, GIS: gastrointestinal system

J Acad Res Med 2020;10(3):220-6

with trisomy karyotype had isolated urinary system abnormalities, while the other 11 (82.4%) patients had additional abnormalities. Considering the presence of additional anomalies in patients with normal or trisomy as a result of karyotype, the difference was statistically significant (p=0.004) (Table 4).

Of fetuses with urinary system anomalies; Due to the fact that the result of karyotyping procedure performed in 10 of them was aneuploidy, due to the fact that 4 had bilateral renal agenesis, and 5 had normal karyotype results but other system anomalies accompanying it, a total of 19 cases (6.7%) were terminated by the decision of the perinatology council (Table 5). In 4 cases with aneuploidy as a result of karyotype, pregnancies continued with the decision of families.

The number of patients who can be followed up in the pediatric surgery clinic/outpatient clinic in the postnatal period is 82, and when the cases that go to termination are excluded, the rate is 34.6%. During follow-up, 21 cases with HN regressed spontaneously, 19 cases were diagnosed with VUR, 9 of them operated, 14 cases underwent surgery due to ureteropelvic junction stenosis, 2 cases of PUV and 1 case of ureterovesical obstruction, and 11 cases are still being followed. Eight of the patients who were diagnosed with unilateral MCDK in the prenatal period came for follow-up in the postnatal period and the diagnosis was confirmed in these cases. Six of the cases with prenatal unilateral renal agenesis were controlled in the postnatal period and the diagnosis was confirmed in all of them. Ectopic kidney in 6 cases, duplication of the collecting system in 2 cases, and PUV diagnosis in 1 case were confirmed. The case with PUV diagnosis was operated.

Table 3. Karyotyping technique and results

Karyotyping technique	**n**	**%**
AC	37	74
CVS	8	16
CS	5	10
	50	100
Karyotype result	**n**	**%**
Normal	34	68
Trisomy 21	8	16
Trisomy 18	2	4
Trisomy 13	2	4
Trisomy 16	1	2
Triploidy (69XXX)	1	2
Other (PKHD1)	2	4
	50	100

AC: amniocentesis, CVS: chorionic villus sampling, CS: cordocentesis

Table 5. Karyotype analysis of termination cases

Karyotype technique	**n**	**%**
AC	11	57.9
CVS	4	21
None	4	21
	19	100
Karyotype result	**n**	**%**
Normal karyotype	5 (1*)	33.3
Tr-21	5	33.3
Tr-18	2	13.3
Tr-13	1	6.7
Tr-16	1	6.7
Triploidy (69XXX)	1	6.7
	15	100

*PKHD1 (+) case, AC: amniocentesis, CVS: cardiovascular system

Table 4. Comparison of normal and trisomy group according to karyotype result

	Normal karyotype group (n=34)	**Trisomy group**	**p***
Age	(n=13)	p*	0.667
Gestational week	19±3	21±6	0.165
Termination	5	9	0.002
Presence of additional anomaly	1	5	0.004
Anomaly	-	-	-
Unilateral hydronephrosis	10	4	0.109
Bilateral hydronephrosis	13	3	0.012
Megasistis	5	5	1
Unilateral MCDK	2	-	-
Bilateral MCDK	1	-	-
Bilateral renal agenesis	1	-	-
Ectopic kidney	1	-	-
Duplication of collector system	1	-	-
Extrophia vesica	-	1	-

*P<0.05, MCDK: multicystic dysplastic kidney

J Acad Res Med 2020;10(3):220-6

DISCUSSION

Fetal HN is a common finding in antenatal ultrasonography observed in 0.6-4.5% of pregnancies and 20-40% of the cases are bilateral (11). The rate of cases with bilateral HN in our study was 43%, which is consistent with the literature. Most cases of fetal HN are clinically benign and temporary. Temporary HN occurs in 41-88% of cases, is associated with temporary stenosis in the ureteropelvic junction at an early stage and improves as the fetus matures (12). No criteria have been defined that can identify all newborns with significant pathology, and exclude infants with transient/physiological HN. Although a low threshold value (RPD >4 mm) in the second trimester has more sensitivity in detecting babies with CAKUT, it will include a large number of cases that are subjected to unnecessary tests and without kidney disease. In addition, RPD can be affected by gestational week, fetal bladder distension, and maternal hydration. In a study involving 74 cases with fetal HN in 2005 (13), spontaneous resolution was observed in the postnatal period in 74% of cases, which was found to be 56.5% for cases of unilateral HN and 46.2% for cases of bilateral HN in our study. In HN cases; the severity of HN, its being unilateral or bilateral, the presence of associated renal and extrarenal anomalies, gestational age and assessment of amniotic fluid status can give more insight into the postnatal process.

When the causes of chronic renal failure (CRF) in childhood are examined, it is seen that urinary system malformations have an important place. In order to reduce the incidence of CRF, it is very important to recognize these malformations in the early period, to make appropriate follow-up and treatment. The detection rate of bilateral renal agenesis in the prenatal period is 84-91%. In these cases, the fetal kidneys, ureters and bladder are not ultrasonographically monitored and the cases are accompanied by oligo-anhydramnios (14,15). In our study, 4 cases of bilateral renal agenesis diagnosed in the prenatal period were terminated by the decision of families and in 3 cases the diagnosis was confirmed after termination, and in 1 case, ventricular septal defects and micrognathy were additionally detected. In cases of bilateral renal agenesis, oligo-anhydramnios is the most difficult condition to detect additional anomalies in the prenatal period. The diagnosis of unilateral renal agenesis is more likely to be skipped during the prenatal period due to normal amnion fluid and bladder volume. The diagnosis depends on the correct exclusion of the presence of a second kidney in the renal fossa or ectopic region. Prenatal detection rate for unilateral renal agenesis is 59-80% (14). In our study, 6 of the 8 cases diagnosed with unilateral renal agenesis in the prenatal period were evaluated in the postnatal period and the diagnosis was confirmed. MCDK occurs with a frequency of 1/3,600-4,300. Although the disease can involve both kidneys, most cases are unilateral, and the left kidney is more frequently affected (16). In our study, 15 cases were diagnosed with unilateral MCDK in the prenatal period, and 8 cases were confirmed in the postnatal period. In 5 of these 8 patients who continued their follow-ups, involution occurred in the multicystic kidney, and a compensatory hypertrophy developed in the contralateral kidney. In addition, VUR developed in the contralateral kidney in 1 case. VUR is the most common renal abnormality in the contralateral kidneys of patients with MCDK and this rate is 21% (17).

Studies that identified HN in the second trimester as RPD >4 mm showed that HN (18%) was higher in fetuses with Down syndrome compared to normal control group fetuses (0.5-3%) (18,19). For this reason, it is used as a marker in fetal aneuploidy screening, but there is no indication of chromosome analysis alone. However, it should be known that it increases the risk of age-related chromosome anomaly 1.5 times and prenatal counseling service to be given to pregnant women should be planned accordingly. In a study involving 375 cases with isolated HN, the incidence of Down syndrome was found to be 0.53% (20). Another study involving 682 fetuses with renal defects found that the incidence of chromosomal abnormalities was 13% (21). The incidence of aneuploidy in isolated bilateral renal agenesis was 5%, and the incidence of aneuploidy in the presence of additional abnormalities in patients with unilateral and bilateral renal agenesis was 33% and 40%, respectively. In addition, the most common chromosomal abnormalities in renal agenesis and MCDK cases are Tr-13 and Tr-18 (21). In our study, the proportion of fetuses with chromosomal abnormalities was 6.2% when cases where karyotyping was recommended but refused to perform were excluded. The most common group in which we recommend karyotyping is the group with a combination of unilateral HN and additional abnormalities, while the most common chromosomal anomaly in this group is Down syndrome. While being a reference center for prenatal diagnosis made it easier for us to catch fetuses with chromosomal abnormalities, anxiety about possible complications of karyotyping and, as a result, rejection of the procedure was our main limitation.

When urinary system anomalies are detected in the ultrasonography performed during prenatal period, other systems should also be carefully scanned. Because urinary system anomalies are mostly found together with other system anomalies. In addition, in cases with urinary system anomalies, in the presence of additional anomalies, the risk of chromosomal anomaly is increased. In the study of Hürcan et al. (22), the rate of fetuses with other congenital malformations accompanying urinary system anomalies was found to be 61.7%, and 23.6% in the study of Batukan et al. (23). In our study, the presence of other accompanying congenital anomalies was found to be 18.8%. Both in the study of Hürcan et al. (22) and in our study, the most common accompanying anomalies were central nervous system anomalies. The high proportion of accompanying anomalies in our study group was consistent with the literature.

In cases where severe uteroplacental insufficiency and early membrane rupture are excluded, if the bladder cannot be monitored with oligo-anhydramnios on ultrasound, it is considered that there is no functional kidney tissue. In this case, the first things that should come to mind for diagnosis are bilateral renal agenesis, bilateral MCDK disease or infantile PCK disease. Distinguishing these diseases from each other is possible only with detailed ultrasonographic examination. Long-term absence

J Acad Res Med 2020;10(3):220-6

of amniotic fluid in these cases causes pulmonary hypoplasia, which leads to severe respiratory failure at birth. In the study of Balsak et al. (24), the termination rate in cases with urinary system anomalies was found to be 14%, and fetuses with PCD disease were the first. In our study, 6.7% of the cases were terminated and bilateral renal agenesis, aneuploidy and PCK disease were the main causes. The fact that the number of fetuses with urinary system abnormalities was higher in our study was evaluated as the main cause of the difference.

In fetuses with sonographic findings compatible with lower urinary tract obstruction, there is no clear evidence that prenatal vesicoamniotic shunt administration improves renal function and long-term patient survival in prospective and retrospective studies. In addition, it was observed that the complication rate associated with the procedure was 45% (10,25). For these reasons, vesicoamniotic shunt is not performed in our clinic during the prenatal period. In addition, since chromosomal abnormalities are detected in about 25% of cases with urethral obstruction, karyotype analysis is required before treating cases (21). Intrauterine treatment is not recommended as more complex urethral anomalies are seen in female fetuses and the chance of success is lower. If intervention is to be made during antenatal period; the parents should be informed in detail about the risks and benefits of the procedure, neonatal survival and kidney results, and the procedures should be performed by experts.

In postnatal evaluations, the proportion of cases with spontaneous resolution HN was 30.8%, the most common causes of transient HN are VUR and obstruction in the ureteropelvic junction. In a study of Barbosa et al. (26) involving 1,034 cases of fetal HN, the rate of spontaneous resolution in the postnatal period was reported as 25%. The proportion of our patients who underwent surgery in the Postnatal period is 38.2%. Surgical indications were determined as recurrent febrile urinary tract infections and decreased relative kidney function in serial kidney scans. A study published in 2016 found that fetuses diagnosed with HN had a surgical intervention rate of 47% in the postnatal period (27). Both spontaneous resolution and surgical intervention rates of fetuses with HN in the postnatal period were found to be consistent with the literature.

CONCLUSION

Abnormalities of the urinary system can be detected mostly by ultrasonography in the prenatal period, and can be associated with chromosomal abnormalities and other structural malformations. Appropriate diagnosis, follow-up and treatment of these anomalies with a wide clinical spectrum, both in the prenatal period and in the postnatal period with a multidisciplinary approach, is of great importance.

Ethics Committee Approval: Ethics Committee of Karadeniz Technical University Faculty of Medicine, (decision number: 2019/28).

Informed Consent: Written and verbal information was given to the families about the method of karyotyping and possible complications, informed consents were obtained.

Peer-review: Externally peer-reviewed.

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Visual Evoked Potentials in Euthyroid Hashimoto's Thyroiditis

Hakan Şilek[1], Rengin Bilgen[1], Bahar Erbaş[2,3]

[1]Yeditepe University Faculty of Medicine, Department of Neurology, İstanbul, Turkey
[2]Demiroğlu Bilim University Faculty of Medicine, Department of Pharmacology, İstanbul, Turkey
[3]İstanbul Florence Nightingale Hospital, Clinic of Neurology, İstanbul, Turkey

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ABSTRACT

Objective: Hashimoto's thyroiditis (HT) is an autoimmune disease in which neurological involvement is not uncommon. This study aimed to explore the presence of visual evoked potential (VEP) changes as an indicator of subclinical central nervous system involvement in euthyroid HT patients without obvious neurologic findings.

Methods: Thirty HT patients with normal neurological examination and thirty healthy controls were included. VEPs were recorded by using pattern-reversing black and white checkerboard with monocular testing. P100, N75 and N135 (ms) peak latencies, and P100 amplitudes of right (R) and left (L) eyes in each group were compared.

Results: There was no significant difference between the groups for age. The mean of the P100 (R: 108.13±4.3, L: 108.2±4.4 ms), N75 (R: 79.23±6.03, L: 80.2±5.78 ms) and N135 (R: 141.8±11.2, L: 142.4±10.2 ms) latencies, and the P100 amplitude (R: 6.71±4.16, L: 6.6±3.9 μV) in the HT group were not significantly different from P100 (R: 107.2±3.8, L: 107.7±4.36 ms), N75 (R: 79.9±5.5, L: 78.9±6.17 ms), N135 (R: 140.3±8.4, L: 141.9±9.7 ms) latencies and P100 amplitude (R: 8.20±3.32, L: 6.9±2.9 μV) in the control group. Also, there was no significant correlation between P100 latencies and thyroid specific antibody levels in the HT group.

Conclusion: This result may be due to the fact that HT does not significantly affect the optic nerve and visual pathways, or that VEP is an inadequate technique to demonstrate possible involvement.

Keywords: Hashimoto's thyroiditis, visual evoked potentials, P100, N75, N135

INTRODUCTION

Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis or autoimmune thyroiditis may be associated with various neurological disorders, presenting as central and/or peripheral nervous system involvement (1-3). The detection of an increase in serum anti-thyroid peroxidase antibody (TPOAb) and anti-thyroglobulin antibody (TgAb) levels in this autoimmune disease is important for making the diagnosis. Hashimoto's encephalopathy (HE) is the most remarkable example of a central nervous system (CNS) involvement linked to HT (3). It has been shown that demyelinating lesions similar to multiple sclerosis (MS) and single-photon emission computed tomography abnormalities can be seen in HT (4,5). Furthermore, brain function abnormalities such as cognitive and affective disturbances have also been reported in euthyroid HT patients with subtle neurological symptoms (6).

ORCID IDs of the authors: H.Ş. 0000-0002-6550-6200; R.B. 0000-0002-5138-971X; B.E. 0000-0002-6125-7761

Corresponding Author: Hakan Şilek,
E-mail: hakan.silek@yeditepe.edu.tr

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In many diseases of the CNS, particularly in demyelinating diseases, the visual system can be affected subclinically (7,8). Visual evoked potential (VEP), a gross electrical signal recorded from the visual cortex in response to a changing visual stimulus on the check-board pattern (pattern onset/reversal VEP), is one of the methods used to demonstrate the overt or subtle dysfunctions of the visual system (9).

This study aimed to explore the presence of VEP changes as an indicator of subclinical CNS involvement in euthyroid HT patients without obvious neurologic findings.

METHODS

The participants of the patient group (HT group) were randomly selected (by simple randomization according to their protocol numbers) from the patients (over 18 years old) who were admitted to the neurology outpatient clinic from January to March 2019 with non-specific complaints and an HT diagnosis confirmed by an endocrinologist. All the patients had high TPOAb (>34 IU/mL) and TgAb (>115 IU/mL) levels, reduced echogenicity of the thyroid parenchyma on thyroid ultrasonography, normal thyroid function tests, and no objective finding on the neurological examination. The control group consisted of healthy volunteers. The participants with ocular diseases that could affect the VEP test, such as glaucoma, were excluded from the study. None of the participants had visual complaints.

All participants underwent neurologic examination, and visual acuity was measured using a Snellen chart. Thyroid stimulating hormone (TSH), free thyroxine (fT4), TPOAb, and TgAb levels in the last three months were obtained retrospectively from the patient records.

VEPs were performed by the same technician, in the neurophysiology laboratory, using the 10/20 system monocular reverse pattern VEP method, with Keypoint G4 (Natus Medical Incorporated Alpine Biomed Apps Skovlund, Denmark). The VEP study protocol was based on the recommendations of the International Society for Clinical Electrophysiology of Vision on performing VEPs (10). The active electrode (Oz) was placed in the midoccipital line, 5 cm superior to the inion. The reference VEP has been used in clinical neurology, for the electrode (Fz) was in the mid frontal line and the grounding electrode was at the vertex (Cz). Visual stimulation was provided by a pattern generator monitor with a mean luminance of 50 cd/m^2, full field size 15°, and each check subtended 60' and 15'. The mean luminance in the test room was kept at 80 cd/m^2, the contrast between the black and white squares was 85%. The sweep speed, sensitivity and sweep duration and bandpass filters were 30 ms/division, 5 microV/division, 300 ms, and 2-100 Hz, respectively. The subjects were asked to sit on a chair at a distance of 100 cm from the monitor, close one eye at a time while looking at a fixed point in the middle of the monitor, and relax. The rate of pattern reversal was 2 Hz and an average of two sets of 200 responses was recorded. Both eyes were separately tested.

Latencies (ms) of the major positive component (P100) and negative peaks (N75 and N135) and P100 amplitudes (μV) were determined. Abnormal P100 latencies were normally considered when the latency exceeding 2.5 to 3 SD beyond the mean, or beyond the 95th to 99th percentile. The laboratory values for P100 latency, determined previously in 28 healthy, 21-to 63-year-old controls, is 101.3±6.2 ms (mean ± standard deviation), and therefore, the normal limit is <116 ms (unpublished data). The VEP tests of the participants were evaluated by the same investigator who was blinded to the groups.

This study was approved by Yeditepe University Faculty of Medicine Local Ethics Committee (approval number: 2019-920, date: 02.01.2019) and written informed consents were obtained from all participants.

Statistical Analysis

The sample size was determined by using the G*Power software within the inputs of α err prob: 0.05, Power (1-β err prob): 0.80, and the effect size d=0.8 before the initiation of the study (11). SPSS 22.0 program was used for the analysis. The distribution of the variables was evaluated using the coefficient of variation, skewness-kurtosis, histogram and the Shapiro-Wilk normality test. Independent Samples t-test was used to compare the VEP values (P100, N75 and N135 waves, and amplitude of P100) of two groups (the right eye values of the patients were compared with the right eye values of the control group and the left eye values were compared with the left eye of the other group). The correlation between the P100 latencies and thyroid antibody levels in the HT group was evaluated using the Pearson correlation test. A p-value less than 0.05 was considered to be statistically significant.

RESULTS

Thirty HT patients and 30 control were included. Since all the patients were females, the control group was also composed of female volunteers. The reasons for and frequencies of the referral of the patients to the neurology clinic were as follows: Headache 18 (60%), mild cognitive complaints (forgetfulness, decreased attention, and difficulty in concentration) 6 (20%), sleep disturbances 3 (10%), fatigue 2 (6.7%) and dizziness 1 (3.3%). There was no significant difference in age between the HT and control groups (38.93±8.73 and 33.80±8.77 years, respectively). The mean duration of HT disease was 11.68±8.89 years.

Mean serum TSH, fT4, TPOAb, and TgAB levels of HT patients were 2.7±1.88 uIU/mL, 1.16±0.21 ng/dL, 349.7±204.9 IU/mL, and 192.09±168.16 IU/mL, respectively. The visual acuities of all participants were 20/20.

Table 1 shows the comparisons of the mean latencies of P100, N75, and N135 waves, and P100 amplitudes of R and L eyes in the HT and control groups. There was no statistical difference between the latencies of the abovementioned waves and amplitudes between the two groups. In the HT group, P100 wave latencies were not significantly correlated with the levels of TPOAb (r=0.08, p=0.71) and TgAb (r=-0.13, p=0.710).

J Acad Res Med 2020;10(3):227-31

Table 1. The comparison of VEP latencies (P100, N75, N135) and P100 amplitudes of the HT and control groups

VEP	SIDE	HT (mean ± SD)	Control (mean ± SD)	p
P100 latency (ms)	R	108.13±4.3	107.2±3.8	0.412
	L	108.2±4.4	107.7±4.36	0.662
N75 latency (ms)	R	79.23±6.03	79.91±5.50	0.620
	L	80.20±5.78	78.90±6.17	0.438
N135 latency (ms)	R	141.8±11.2	140.30±8.41	0.630
	L	142.4±10.2	141.91±9.72	0.869
P100 amplitude (μV)	R	6.71±4.16	8.20±3.32	0.579
	L	6.6±3.85	6.92±2.90	0.709

VEP: visual evoked potentials, R: right eye, L: left eye, SD: standard deviation, ms: miliseconds, μV: microvolt, Independent Samples t-test, HT: Hashimoto's thyroiditis

DISCUSSION

Autoimmunity targeting the thyroid gland can also influence the CNS, and this association has been demonstrated by immunohistochemistry and imaging techniques (12-15). Animal models have shown that immune system activation can trigger inflammation in the CNS and influence animal behaviors (16). The effects of immune dysregulation on the CNS can be explained by the altered neural pathway functions and the blood-brain barrier damage as a result of the changes in various cytokines (17,18). Positive glucocorticoid response and histologic findings of perivascular lymphocytic infiltration in HE, the more overt CNS involvement of HT, may support the hypothesis based on the immunological explanation (19). Furthermore, *in vitro* studies showed that various antibodies, such as anti-ganglioside, anti-neural antibodies, and particularly TPOAbs, bind to CNS cells and impair myelin sheath damaging myelinogenesis (6,20). The increased production of monocyte- and T-lymphocyte-derived cytokines in HT patients can also negatively affect some neurotransmitters playing role in various neuronal pathways (6).

In recent years, an increasing number of studies have reported insidious brain function abnormalities, only detected by specific tests, in euthyroid patients (6,21-23). Immunological mechanisms are the most probable reasons for these abnormalities, as shown by the studies indicating that TPOAb levels are higher in the patients with cognitive deficits than in the other HT patients without abnormalities (6,22,23).

HT, the most common autoimmune thyroid disease, may also coexist with other autoimmune conditions (24,25). In the context of this study, it is important that HT and autoimmune diseases of the CNS affecting the optic nerve and visual pathways, such as MS, are remarkably seen together. Since HE has several features resembling MS, such as common genetic loci, certain deregulated anti-inflammatory responses, elevated CSF oligoclonal bands, and demyelinating lesions on imaging studies, it is included in the differential diagnosis of MS, and both diseases have been suggested to have common similar pathological pathways in CNS involvement (2,5,19,24,26).

The involvement of the optic nerve and visual pathways in autoimmune CNS disorders can be seen sub-clinically, as in MS, and is only demonstrated by special methods such as VEP (7,8). The hypothesis of our study was based on this information. Moreover, it has been shown that patients with recurrent and bilateral optic neuritis have a greater frequency of HT than other optic neuritis patients, despite normal magnetic resonance imaging (MRI) findings (27). In many cases, optic neuropathy in autoimmune thyroid diseases relates not only to thyroid hormones, but also to increased autoantibodies and can be seen in euthyroid patients (28).

VEP parameters, particularly latencies, may be influenced by hypothyroidism and hyperthyroidism. Although this situation is well documented in hypothyroidism, controversial results have been reported in hyperthyroidism (29-31). The prolongation of VEP latencies is the most common change, and it usually returns to the normal after the euthyroid state is achieved with the treatment in hypothyroid patients (32-34). Thyroid ophthalmopathies and exophthalmos are the main reasons of the VEP changes in hyperthyroid patients (29,33,35). While the exact mechanisms remained elusive, compressive optic neuropathy, axoplasmic stasis, ischemia and mechanical stretch due to proptosis, and perineural inflammation have been proposed (33,36). Decompressive surgical approaches and steroid treatment can greatly improve the VEP changes in hyperthyroid patients with ophthalmopathy (37,38).

Our goal was to explore the presence of VEP changes as an indicator of the subclinical effects of HT on optic nerve and visual pathways. The pattern reversal VEP consists of a prominent positive component at approximately 100 ms (P100), followed by negative components (N75 and N135). Dysfunctions of the optic nerve, chiasma, and retrochiasmal pathways can be assessed using the VEP. Although a delayed P100 component often occurs in association with optic nerve diseases, it should not be considered pathognomonic for optic nerve diseases (29). VEP can be used to detect subclinical optic nerve demyelination. Even after the use of MRI increased, the VEP preserved its value in the diagnosis of demyelination because it has been shown that the specificity

of the changes on MRI may be less than originally anticipated in many patients (39).

Study Limitations

We could not find any statistically significant difference between the groups in terms of the latencies of VEP waves and P100 amplitudes. These results may be due to the fact that the optic nerve and visual pathways are not significantly affected in euthyroid HT patients or the sensitivity of VEP is not sufficient (8,40). There are some limitations of this study. The small number of patients and the lack of male euthyroid HT patients are some of our limitations.

CONCLUSION

The results of this study cannot support the hypothesis that VEP can be a screening test for the subclinical involvement of the optic nerve or visual pathways in euthyroid HT patients. As the possible reasons for these results, we suggested that there was no significant involvement in the aforementioned regions of CNS in euthyroid HT patients without visual symptoms and/or the lack of sufficient sensitivity of the VEP method in this regard.

Ethics Committee Approval: This study was approved by Yeditepe University Faculty of Medicine Local Ethics Committee (approval number: 2019-920, date: 02.01.2019).

Informed Consent: Written informed consents were obtained from all participants.

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Rare Factor Deficiencies: A Retrospective, Single-center Cohort Study

Nilgün Eroğlu[1], Erol Erduran[1], Ayşenur Bahadır[1], Haluk Saruhan[2]

[1]Karadeniz Technical University Faculty of Medicine, Department of Pediatric Hematology and Oncology, Trabzon, Turkey
[2]Karadeniz Technical University Faculty of Medicine, Department of Pediatric Surgery, Trabzon, Turkey

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ABSTRACT

Objective: Rare factor deficiencies (RFD) include fibrinogen and factor (F) II, FV, combined FV and FVIII, FVII, FX, FXI, and FXIII deficiencies. Although patients with RFD may present with severe hemorrhage, little is still known about this patient group. Additionally, mortality and morbidity also increase due to the limited available knowledge concerning diagnostic and therapeutic methods and surgical approaches. Herein, we report the demographic features, clinical follow-up, surgical approaches, and treatment of patients with RFD.

Methods: We retrospectively evaluated 37 patients with RFD. Patients' demographic characteristics, age at presentation, type of bleeding at diagnosis, clinical findings, surgeries performed, and surgical approaches were recorded.

Results: In this study, 64.8% of the patients were males and 35.2% were females. The most common factor deficiency was FVII deficiency (29.7%). Parental consanguinity was detected in 48.6% of cases. Adenoidectomy was performed on 27% of patients with FVII deficiency. Circumcision was performed on 67% of patients with FXI deficiency, 27% of patients with FVII deficiency, and 20% of patients with FV deficiency. Fresh frozen plasma, fibrinogen concentrate, or rFVIIa combined with tranexamic acid were administered before surgery. No post-operative complications were observed.

Conclusion: RFDs are prevalent due to the increased frequency of consanguineous marriages, and the diagnosis of coagulation disorders is substantially delayed in Turkish children. Since the clinical findings of RFDs are not obvious, patients in the preoperative period must be assessed with RFD in mine. We think that this paper will contribute to the diagnosis and treatment of RFD and to the surgical approaches.

Keywords: Rare factor deficiencies, surgery, factor

INTRODUCTION

Rare factor deficiencies (RFDs) include congenital fibrinogen and factor (F) II, FV, combined FV and FVIII, FVII, FX, FXI and FXIII deficiencies other than hemophilia A, hemophilia B, and von Willebrand's disease. A deficiency in any of the above-mentioned coagulation factors may result in a coagulopathy, leading to either spontaneous or post-traumatic and post-operative hemorrhages. Deficiencies of FVIII and FIX, also known as hemophilia A and B, are the most common, with a prevalence of 1:5,000 and 1:30,000 males, respectively; together with von Willebrand's disease, they account for 95%-97% of all coagulopathies (1). On the other hand, the remaining deficiencies, known as rare coagulation disorders (RCDs), are much less prevalent, with rates ranging from 1:2 million for FII and FXIII deficiencies to 1:500,000 for FVII deficiency, in the general population (2). However, all these RCDs represent an

ORCID IDs of the authors: N.E. 0000-0002-9956-4054; E.E. 0000-0003-1011-5111; A.B. 0000-0001-9226-369X; H.S. 0000-0002-0991-8235.

Corresponding Author: Nilgün Eroğlu,
E-mail: dr-nilguner@hotmail.com

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important challenge for clinicians, especially in countries where consanguineous marriages are frequent. RCDs are characterized by a wide variety of symptoms ranging from mild to severe, which can vary significantly from one disorder to another and from one patient to another. Generally, the most typical symptoms of all RCDs include mucosal tract bleedings and excessive bleeding during invasive procedures, delivery in women, and circumcision in boys. In addtion, other life- and limb-endangering symptoms such as central nervous system (CNS) bleeding and hemarthroses are mostly present only in afibrinogenemia and FX and FXIII deficiencies (3). This clinical heterogeneity, combined with the smaller number of patients affected with RCDs compared with hemophilias, led to a lack of studies that aim to understand how to recognize and diagnose a RCD. As a result, this lack of knowledge led to a delay in the design and production of adequate therapeutic treatments for RCDs.

The purpose of this retrospective study was to describe the demographic features, clinical follow-up and treatment of patients with RFD.

METHODS

Thirty-seven cases of RFD that were followed up and treated at our clinic between 2006 and 2019 were retrospectively analyzed. Information was obtained from the patients' files. Patient characteristics as well as family history, age at presentation, first bleeding symptoms and bleeding episodes, treatment of bleeding episodes, prophylactic treatments, and surgical approaches applied were recorded. The first coagulation screening tests were performed using prothrombin time (PT) and activated prothrombin time (aPTT). Specific factor deficiency and inhibitor levels were investigated for the cases according to the results of the PT or aPTT tests. FXIII levels were evaluated qualitatively by screening for the lysis of formed clots in 5 mol/L of urea without prolonged PT and aPTT in patients with hemorrhagic diathesis. Patients with factor activities lower than 50% were included in the study. Values under 100 mg/dL were defined as hypofibrinogenemia.

Statistical Analysis

Simple descriptive analyses, including mean, median, and range, were used to summarize the results using SPSS version 19 (SPSS Inc., Chicago, IL).

RESULTS

In this study, 64.8% of the patients were males and 35.2% were females. Patients' demographic characteristics and age at presentation are shown in Table 1. The distribution of RFD is shown in Figure 1. The most common factor deficiency was FVII deficiency (29.7%) (Figure 1). Parental consanguinity was found in 48.6% of cases. Parental consanguinity rates were 100% in fibrinogen deficiency and 66.6% in FXI deficiency. Factor levels were less than 5% in 18.7% of patients, 5%-30% in 43.7% of patients, and 30%-50% in 37.5% of patients. Factor levels were

Table 1. Patients' demographic characteristics

	Fibrinogen deficiency	FV deficiency	FV + FVIII deficiency	FVII deficiency	FX deficiency	FXI deficiency	FXIII deficiency	Total
Patients	5 (13.5%)	5 (13.5%)	1 (2.7%)	11 (29.7%)	4 (10.8%)	6 (16.2%)	5 (13.5%)	37
Sex								
Male	2	4	-	10	-	5	3	24 (64.8%)
Female	3	1	1	1	4	1	2	13 (35.2%)
First bleeding time								
<1 year	5	1	-	2	1	-	-	9 (24.3%)
1-5 year	-	-	-	2	3	3	5	13 (35.1%)
>5 year	-	4	1	7	-	3	-	15 (40.5%)
Consanguinity	5	1	1	4	2	4	1	18 (48.6%)
Factor activity							Factor activity can not be measured	
<5%	2	-	-	-	2	2		6
5%-30%	-	3	-	7	2	2		14
30%-50%	3	2	1	4	-	2		12
Clinical symptoms								
Grade 1	-	-	-	7	1	2	1	11 (29.7)
Grade 2	1	1	1	-	1	-	1	5 (13.5%)
Grade 3	4	4	-	4	2	4	3	21 (56.7%)
Asymptomatic	-	-	-	-	-	-	-	-
Prophylaxis	2	-	-	1	1	-	-	4 (10.8%)

undetectable in five patients with FXIII deficiency. Fibrinogen levels of the hypofibrinogenemia patients were below 100 mg/dL (74 mg/dL in one, 50 mg/dL in one, and 40 mg/dL in three). FV and FVIII levels in a patient with combined FV and FVIII deficiency were 35% and 28.7%, respectively. Moderate FVII deficiency was determined in 18.9% of patients and mild deficiency in 10.8%. Moderate or severe factor X deficiency was determined in 10.8% of patients, and mild, moderate, or severe FXI deficiencies in 16.2%. Grade 1 bleeding symptoms (Bleeding that occurred after trauma or drug ingestion) were observed in 29.7% of symptomatic patients, grade 2 symptoms (Spontaneous minor bleeding: bruising, ecchymosis, minor wounds, oral cavity bleeding, epistaxis, and menorrhagia) in 13.5%, and grade 3 (Spontaneous major bleeding: hematomas, hemarthrosis, CNS, GI, and umbilical cord bleeding) in 56.7%. Life-threatening CNS bleeding was determined in four patients with RFD after trauma. Ecchymosis and epistaxis were most frequently detected in FVII deficiency at a level of 18.9%. The gastrointestinal system (GIS) bleeding rate was determined as 8.1% in fibrinogen and FV deficiencies. The type of bleeding at diagnosis and clinical findings are shown in Table 2, while the surgical procedures performed are shown in Table 3. Adenoidectomy was performed on 27% of patients with FVII deficiency. Circumcision was performed on 67% of patients with FXI deficiency, 27% of patients with FVII deficiency, and 20% of patients with FV deficiency. Fresh frozen plasma (FFP), fibrinogen concentrate, or rFVIIa in combination with tranexamic acid were administered before surgery. Tranexamic acid was initiated in patients who were to undergo circumsion, adenoidectomy, and undescended testis surgery and in those with mucosal bleeding, in three doses of 10 mg/kg/dose iv 8 h before surgery, and was maintained for two or three days after the surgery depending on

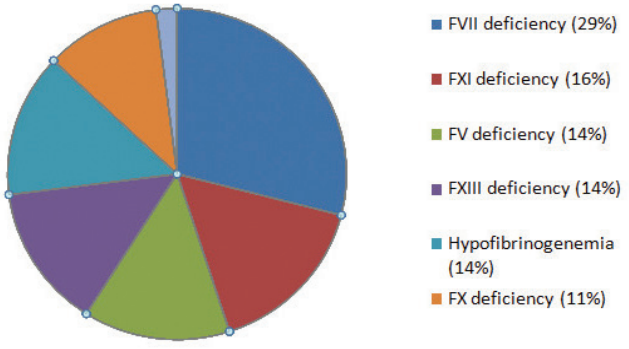

Figure 1. Distrubition of rare factor deficiencies

Table 2. Patients' clinical manifestations

	Fibrinogen deficiency (N:3)	Fibrinogen + FXIII deficiency (N:2)	FV deficiency (N:5)	FV + FVIII deficiency (N:1)	FVII deficiency (N:11)	FX deficiency (N:4)	FXI deficiency (N:6)	FXIII deficiency (N:5)
Ecchymosis n (%)	2 (5.4)	2 (5.4)	1 (2.7)	1 (2.7)	3 (8.1)	2 (5.4)	2 (5.4)	2 (5.4)
Epistaxis n (%)	2 (5.4)	2 (5.4)	1 (2.7)	1 (2.7)	4 (10.8)	2 (5.4)	2 (5.4)	1 (2.7)
Umbilical bleeding n (%)	2 (5.4)	2 (5.4)	1 (2.7)	-	-	-	-	1 (2.7)
GIS bleeding n (%)	1 (2.7)	1 (2.7)	1 (2.7)	-	-	-	-	-
Muscular hematoma n (%)	-	-	1 (2.7)	-	-	-	-	2 (5.4)
Joint bleeding n (%)	-	-	1 (2.7)	-	1 (2.7)	1 (2.7)	-	1 (2.7)
CNS bleeding n (%)	1 (2.7)	1 (2.7)		-	1 (2.7)	1 (2.7)	-	-

GIS: gastrointestinal system, CNS: central nervous system, N: total number of patients for each factor defiency, n: number of patients with the specific clinical presentation

Table 3. Surgical procedures performed

	Fibrinogen deficiency (N:5)	FV deficiency (N:5)	FVII deficiency (N:11)	FX deficienc (N:4)	FXI deficiency (N:6)
*Circumsion (n, %)	-	1 (20)	3 (27)	-	4 (67)
*Adenoidectomy (n, %)	-	-	3 (27)	-	-
*Undescended testis surgery (n, %)	-	-	1 (9)	-	-
*Humerus fracture surgery (n, %)	-	-	1 (9)	-	-
*ASD surgery (n, %)	1 (50)	-	-	-	-
*Mastoidectomy (n, %)	-	-	1 (9)	-	-
*Mass excision (n, %)	-	-	-	1 (25)	-
*İntracerebral hematoma evacuation, duraplasty (n, %)	-	-	-	1 (25)	-
*Developmental hip dysplasia surgery (n, %)	1 (50)	-	-	-	-

ASD: atrial septal defect, N: total number of patients for each factor defiency, n: number of patients with the specific surgical method

J Acad Res Med 2020;10(3):232-6

bleeding status. Tranexamic acid was not used preoperatively in hematuria patients. No post-operative complications were observed.

DISCUSSION

Since most RFDs are inherited in an autosomal recessive manner, they are more prevalent in countries where consanguineous marriages are common. An autosomal dominant inheritance has been reported in some cases of FXI deficiency and dysfibrinogemia (2). Although there is no national record system in Turkey, Tugcu et al. (4) reported a consanguineous marriage rate of 49.5% in their study of 192 RFDs, similar to the rate of 48.6% in this study.

FVII deficiency has been reported as the most common RFD in studies from Iran, Italy, and North America, and was also the most common RFD in our study, with a rate of 29.7%. Sharma et al. (5) reported FX deficiency as the most common RFD, while it was the fourth most common RFD in our study, with a rate of 10.8%.

Patients with RFD may present with a range of bleeding symptoms, from post-traumatic bleeding to severe attacks during or after birth. In some factor deficiencies, the factor level is directly related to the hemorrhagic risk, although this is not applicable in every case. The first correlation between factor level and bleeding severity in RFD was reported by the EN-RBD based on data from 489 patients in 13 treatment centers in Europe (6). Peyvandi et al. (6) found a strong correlation between bleeding severity and coagulation activity in fibrinogen, combined FV and FVIII, FX, and FXIII deficiencies, while a weak correlation was determined for FV and FVII deficiencies. No correlation was observed between factor level and bleeding severity for FXI deficiency. In the present study, the correlation between bleeding severity and factor level could not determine. The factor level was below 5% in two patients with FX deficiency. A life-threatening CNS bleeding was observed in one patient and intramuscular hematoma in the other. The factor level was between 30% and 50% in one patient with combined FV and FVIII deficiency, and no bleeding other than grade 1 bleeding was observed in this patient.

CNS bleeding was observed in one of the two patients with hypofibrinogenemia and pericardial tamponade in the other, despite the administration of fibrinogen concentrates and FFP before surgery.

Hemarthrosis and intramuscular bleeding are the most common symptoms in patients with hemophilia, while mucocutaneous bleeding is more common in RFDs (7). In our study, CNS, GIS, umbilical bleeding, hemarthrosis, and hematomas (grade 3 bleeding) were the most common bleeding symptoms (55.2%). RFDs are generally diagnosed after bleeding, and 40% of patients were diagnosed at an age >5 years.

Male children in various societies, including Turkey, have been circumcised for thousands of years for religious and cultural reasons. The known risk of circumcision in normal children is 0.2%-0.6%, but it constitutes a life-threatening risk in children with bleeding disorders (4). The families of children with bleeding disorders wish to see their children circumcised despite the known risks. This is an important ritual for most patients and their families, and is actually a social obligation for boys. As with other surgical procedures, appropriate precautions must be taken in children with bleeding disorders. Since there are few available studies on circumcision and surgery in RFD, the centers' clinical experiences are particularly important (8,9). In our study, patients received tranexamic acid 8 h prior to circumcision. While FFP was administered before surgery in cases of FV and FXI deficiency, it was maintained postoperatively depending on the bleeding status. rFVIIa was given to patients with FVII deficiency. Fibrinogen and FFP were administered before atrial septal defect surgery in fibrinogen deficiency, and combined coagulation concentrate (Cofact®) was administered before mastoidectomy in FX deficiency.

Little is known concerning prophylaxis in RFDs. This is only recommended for short-term use or after surgery. Tugcu et al. (4) applied prophylaxis in cases of fibrinogen, FVII, and FX deficiencies. Prophylaxis after severe, life-threatening bleeding reduces morbidity and mortality in RFDs. In our study, prophylaxis was applied to four patients with fibrinogen, FVII, and FX deficienc because of CNS bleeding. Care must be taken with prophylaxis in FX and fibrinogen deficiencies due to the risk of thrombosis.

RFDs can be detected through preoperative screening, clinical symptoms of bleeding, or incidentally. Clinical diagnosis is therefore difficult. There is no therapeutic strategy for RFDs. Investigation of cases in terms of diathesis before surgery and the management of life-threatening bleeding and surgeries are of vital importance.

We believe that the following procedures should be applied for the treatment and prophylaxis of RFDs and in preparation for surgery.

Tranexamic acid was initiated with three doses of 10 mg/kg/dose iv 8 hours before surgeries, such as circumcision, adenoidectomy, and tonsillectomy surgeries and mucosal bleedings, and was maintained for two or three days after surgery depending on the bleeding status.

In fibrinogen deficiency, fibrinogen concentrate was given at a dosage of 30-40 µg/kg/dose, in patients with grade 2,3 bleedings, and half an hour before surgery. After one hour, the patient went for operation with a level of 200 mg/dL.

In FX deficiency, combined coagulation concentrate (Cofact®) was given at 50 units/kg/dose; in FVII deficiency, rFVIIa was given at 30 µg/kg/dose; and in FV, FXI, and FXIII deficiencies, FFP was given at 15 mL/kg/dose, half an hour before surgery. After one hour, the patient went for surgery with appropriate factor level. Factor therapy can be continued for 24-72 hours according to the patient's bleeding condition. Although prophylaxis is controversial in patients with CNS bleeding, our patients have been receiving prophylaxis for approximately 2 years. No complication or bleeding were observed in our patients and, due to this, we think that prophylaxis is appropriate after CNS bleeding.

Study Limitations

This study has some limitations. The longitudinal cohort had a small sample size, and genetic mutation analysis could not be done.

CONCLUSION

In summary, our results demonstrate that the most common RFD is FVII deficiency, followed by FXI deficiency in Turkish children. RFDs are more prevalent in Turkey than in Western countries due to the high parental consanguinity rates, indicating the need to raise public awareness on the risks of consanguineous marriages and to improve access to genetic counseling and testing facilities. Delayed diagnosis and the lack of prophylactic replacement therapy are the main risk factors that increase life-threatening bleedings. The need for a national bleeding disorders registry is indispensable for the collection of accurate data on the number of patients, complications, and treatment statistics in order to plan effective interventions that can improve the quality of care.

Ethics Committee Approval: Retrospective study.

Informed Consent: Written informed consent, approved by our institutional review board, was obtained from all patient.

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Comparison and Analyses of Intraoperative Consultation and Paraffin Section Responses of Ovarian Lesions

Elife Kımıloğlu[1], İrem Yanık[1], Özgecan Gündoğar[1], Sibel Bektaş[1], Süleyman Salman[2]

[1]University of Health Sciences Turkey, Gaziosmanpaşa Health Practice and Research Center, Department of Medical Pathology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Gaziosmanpaşa Health Practice and Research Center, Department of Gynecology and Obstetrics, İstanbul, Turkey

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ABSTRACT

Objective: We aimed to analyze the sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) and the accuracy of frozen section (FS) method and compare the concordance of FS responses and paraffin section (PS) (final histopathological diagnoses) results of the ovarian mass operations in our hospital.

Methods: We retrospectively reviewed the cases of ovarian lesions operated between March 2008 and June 2018 in which FS was requested. In total 205 cases were found and the results were compared. The FS responses and PS results were classified as benign, borderline and malignant. Seventeen cases weren't responded in FS (and left to be diagnosed in PS) and they were left out of the study.

Results: According to the analyses; the sensitivity of benign, borderline and malignant tumors were 100%, 83%, 95%, and the specificity were 98%, 99%, 98%, respectively. The PPV of borderline and malignant tumors were 91%, 92% and the NPV were 98%, 99% respectively. Furthermore; both of their accuracy was 97%. The concordance between the methods was assessed with Kappa test and found as 94% ($p<0.001$).

Conclusion: In our study we showed that even if all of the FS responses didn't match with its PS, FS has a very high rate of consistency. FS is a way to help the surgeon during the operation. However, it must not be forgotten that this method has its own pitfalls and limitations.

Keywords: Ovary, frozen section, paraffin section, diagnosis accuracy

INTRODUCTION

Intraoperative consultation, or more commonly referred as frozen section (FS), plays a crucial part in pathology. FS is especially important during ovarian mass surgeries since radiological imaging and biochemical markers are limited in determining these lesions' malignancy. Intraoperative consultations are performed to help operating surgeons decide the surgical approach.

This study intended to evaluate the concordance of FS responses and paraffin section (PS) (final histopathological diagnoses) results of ovarian neoplasm surgeries conducted in our hospital and to determine the sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV), and accuracy of FS in categorizing ovarian lesions as benign, borderline, and malignant.

ORCID IDs of the authors: E.K. 0000 0002 2708 1272; İ.Y. 0000-0001-6227-1189; Ö.G. 0000 0003 3075 6063; S.B. 0000-0003-0248-9869; S.S. 0000 0001 7090 6105.

Corresponding Author: İrem Yanık,
E-mail: iremyanik@gmail.com

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METHODS

Subjects

The study retrospectively reviewed cases of ovarian neoplasms operated in our hospital between March 2008 and June 2018 in which intraoperative pathology consultation (FS) were done. A total of 205 cases were included. The reports of the pathologists, who were working in our department during this time, were reviewed, and the FS responses and final PS results were grouped accordingly. PS results were grouped as benign (both neoplastic and non-neoplastic lesions), borderline, and malignant (including metastasis cases), and FS responses were grouped as benign, borderline (including "at least borderline" responses), and malignant. Juvenile and adult granulosa cell tumors, which are considered "low potential of malignancy," were included in the borderline group (1).

Seventeen cases with no definitive FS responses were excluded from this study as they have no equivalent PS results.

The study was approved by the Taksim Training and Research Hospital, Clinic Research Ethics Committee (approval number: 89, date: 19.09.2018).

Statistical Analysis

Data were presented as frequency and percentage, and concordance between the methods was evaluated using the Kappa test. Sensitivity, specificity, PPV, NPV, accuracy, and 95% confidence interval were determined. The limit of significance was set at $p<0.05$ and bidirectional. Analyses were conducted using the NCSS 10 program (Kaysville, UT, USA).

RESULTS

During FS, 127 cases were identified as benign, 22 borderline, and 39 malignant. Of the cases, 17 had a definitive response in FS for varying reasons, and they were left to be determined in PS and, therefore, excluded from this study.

PS results showed that there were 126 (67%) benign cases: 62 (33%) non-neoplastic and 64 (34%) neoplastic. Furthermore, 24 (13%) cases were reported as borderline. Finally, 38 cases were diagnosed as malignant, of which 33 (16%) were primary ovarian tumors and 7 (4%) metastases (Table 1).

Of the 17 cases that were left to be determined in PS, 12 were benign, 3 borderline, and 2 malignant.

The PS and FS responses were compared numerically (Table 2), and 1 of the 127 benign cases in FS was later reported as borderline, 2 of the 22 borderline cases were later reported as malignant, and 3 of the 39 malignant cases were later diagnosed as borderline.

In this study, the mean age of all 188 cases was 49.5 years. When all cases were reviewed, 182 of 188 cases, for which a FS response was given, were compatible with the final paraffin diagnoses, and the outcome showed a consistency of 96.8%.

According to statistical analyses (Table 3), the sensitivities of FS responses of benign, borderline, and malignant tumors were 100%, 83%, and 95%, and the specificity results were 98%, 99%, and 98%, respectively. The PPVs of borderline and malignant tumors were 91% and 92%, and NPVs were 98% and 99%, respectively. Also, both tumors have an accuracy of 97%. The concordance between the methods was evaluated using the Kappa test and was 94%±0.03% ($p<0.001$).

DISCUSSION

Intraoperative pathology consultation (or FS) is an essential method that must be done meticulously since it helps surgeons perform optimal operations for patients. The FS method preserves its significance because of non-specific biomarkers, which also frequently result in false positive or false negative results, and limited preoperative radiological imaging in ovarian neoplasm adequacy. Overdiagnosis during FS will extend the operation time, which may increase mortality and morbidity,

Table 1. Numerical distribution of cases

Benign	Non-neoplastic	62 (33%)	126 (67%)
	Neoplastic	64 (34%)	
Borderline	-	-	24 (13%)
Malignant	Primary ovarian	32 (17%)	38 (20%)
	Metastases	6 (3%)	
Total		188 (100%)	

Table 2. Numerical comparison between paraffin and intraoperative consultation result

		Paraffin results			Total
		Benign	Borderline	Malignant	
Intraoperative consultation results	Benign	126	1	0	127
	Borderline	0	20	2	22
	Malignant	0	3	36	39
Total		126	24	38	188

J Acad Res Med 2020;10(3):237-40

Table 3. Statistical analyses of cases classified as benign, borderline, and malignant

	Benign	Borderline	Malignant
Sensitivity (95% GA)	1 (0.97-1)	0.83 (0.63-0.95)	0.95 (0.82-0.99)
Specificity (95% GA)	0.98 (0.91-1)	0.99 (0.96-1)	0.98 (0.94-1)
PPV (95% GA)	0.99 (0.95-1)	0.91 (0.71-0.98)	0.92 (0.80-0.97)
NPV (95% GA)	1 (0.92-1)	0.98 (0.94-0.99)	0.99 (0.95-1)
Accuracy (95% GA)	0.99 (0.97-1)	0.97 (0.93-0.99)	0.97 (0.94-0.99)

PPV: positive predictive value, NPV: negative predictive value

whereas underdiagnosis may require reoperation or cause tumor to spread (2).

Cases that were inconsistent with PS were reviewed, and it was found that errors might have occurred in some steps. The intraoperative consultation process consists of some crucial parts, including proper macroscopic examination and appropriate sampling. Errors in these parts could be avoided by proper training and experience. Tissue freezing can also result in frozen/freezing artifacts, which might cause the cells to look different than in formalin-fixed tissue samples, thus completely altering the diagnoses. Another important step is the staining part, and errors here might cause the nuclei to appear more hyperchromatic than they are. After meticulously performing all these steps, the pathologists should provide a result in the shortest possible time.

In our study, the group classified as benign contained both non-neoplastic and neoplastic lesions. Endometriosis, follicle cysts, corpus luteum cysts, and abscesses were considered non-neoplastic, whereas cystadenomas, cystadenofibromas, mature cystic teratomas, fibromas, thecomas, and fibrothecomas were neoplastic. During FS, the pathologists did not provide a result (left it to be decided in PS) for some of these benign lesions, such as fibromas/thecomas/fibrothecomas.

Of the 127 cases, which were considered benign during intraoperative consultation, only one did not correlate with the final PS report. During consultation, the case appeared "benign" on FS slides and was thought to be a sex-cord stromal tumor. After 24 hours of formalin fixation, more samples were taken. All the PS slides were evaluated both morphologically and immunohistochemically. The final diagnosis was "adult granulosa cell tumor," which is considered "low malignant potential," and in our study, it is classified as borderline tumors.

The correlation in the benign group was 99.2%. Similar to our study, other studies also have high sensitivity to benign lesions: Sukumaran et al. (2) reported 99.2%, Bige et al. (3) 99.2%, and Arshad et al. (5) 95.6% (2-6).

Borderline tumors make up close to 15%-20% of all ovarian malignancies (7). Borderline epithelial tumors and some sex-cord-stromal tumors (which are considered low/unknown malignant potential tumors like adult/juvenile granulosa cell tumors) were included in the borderline group in our study. The borderline group had the lowest concordance and sensitivity rate at 90.9% and 83%, respectively. Similar sensitivity results were reported in other studies: 88.46% (3), 77.8% (4) and 76.2% (5), thus supporting our findings.

During intraoperative consultations, 2 of 22 border lesions were later categorized as malignant in PS. These tumors were large, and only a limited amount of sampling was done from the areas most suspicious for invasion. No evidence of invasion was found in the frozen slides; however, suspicion of malignancy remained. Therefore, they were reported as "at least borderline" during intraoperative consultation. More samplings were performed from macroscopically detected suspicious thickening of the lesion wall and from the papillary appearing areas after the 24 hours formalin fixation. Routine staining limited the number of invasive areas identified, and therefore, these tumors were later reported as malignant during PS.

The remaining 20 cases were compatible. The two cases, which the pathologists classified FS as "at least borderline" may be statistically seen as an error. However, the surgeons knew the possibility of them being malignant during the operation, and they proceeded accordingly. Since sampling problems during FS for borderline tumors are widely known, the term "at least borderline" as a response is supported by other authors (8).

Tempfer et al. (9) collected data from four studies (including their own) and evaluated borderline tumors during FS. Results showed that consistency between FS and PS was observed in 62.8% of the cases. According to them, because of this high ratio of underdiagnosis/overdiagnosis (37.2%), when FS is classified as borderline, surgeons should not take any further action during the operation and wait for PS reports. It is also suggested that for larger lesions (>5 cm), after a thorough macroscopic evaluation, multiple samples might be used to answer FS or intraoperative consultation might not be done at all (9).

An additional observation showed that subspecialization of pathologists in gynecologic pathology yielded better results (9). For example, Bige et al. (3) presented two sets of data from gynecologic and non-gynecologic pathologists and found that percentages of sensitivity, specificity, PPV and NPV were higher in gynecologic pathologists, especially in the borderline group. According to Açikalin et al. (4), gross examination conducted by gynecologic pathologists during FS is an important factor to increase FS accuracy. This factor might be one of the limitations of our study because our department has no subspecialized pathologists.

Other reasons that borderline tumors are challenging to assess during FS include their heterogeneous component and size. Only a limited amount of sampling can be done in FS; however, after fixation, more lesions can be sampled, and this may very well change the diagnosis (2,6,10).

In the malignant group, there were two cases of primary ovarian tumors and metastases. In 36 of the 39 malignant cases, the FS responses and PS results were consistent. However, the remaining three cases were later reported as borderline lesions because the cells that were considered invasive were actually pseudoinvasions and the nuclei appeared more hyperchromatic because of staining and improper sectioning (such as section thickness).

The concordance rate and sensitivity of the malignant group were 92.3% and 95%, respectively. Açikalin et al. (4) and Bige et al. (3) had sensitivities of 95.6% and 95%, respectively, which are similar to our study. However, Sukumaran et al. (2) had a slightly lower sensitivity (82.95%), and Takemoto et al. (10) had slightly higher data (99.2%).

According to statistical findings, a high consistency was found between these methods (Kappa 0.94, $p<0.001$). The benign lesion group had the highest sensitivity and accuracy rates (100% and 99%, respectively), whereas the borderline group had the highest specificity (99%).

CONCLUSION

Although the coherency between FS and PS is not 100%, it is still high, and that is why FS still plays a crucial part in pathology practice. Considering these findings, surgeons must not forget that FS might be limited and have pitfalls; therefore, they should plan their operations accordingly.

Ethics Committee Approval: The study was approved by the Taksim Training and Research Hospital, Clinic Research Ethics Committee (approval number: 89, date: 19.09.2018).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.K., Design - İ.Y., Supervision - E.K., S.S., Resources - E.K., S.B., S.S., Materials - S.S., Data Collection and/or Processing - İ.Y., Ö.G., Analysis and/or Interpretation - İ.Y., Ö.G., Literature Search - S.B., Writing Manuscript - İ.Y., Ö.G., Critical Review - E.K., S.B.

Conflict of Interest: The authors have no conflict of interest to declare.

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Optimal Target in Deep Brain Stimulation for Parkinson's Disease: Comparison of Atlas and Magnetic Resonance Imaging-based Stereotactic Targeting

İdris Sertbaş

İstanbul Yeni Yüzyıl University Faculty of Medicine, Department of Neurosurgery, İstanbul, Turkey

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ABSTRACT

Objective: We aimed to compare magnetic resonance imaging (MRI) and atlas measurements to determine the target coordinates of globus pallidus internus (GPi) and subthalamic nucleus (STN) during stereotactic neurosurgery.

Methods: Eleven patients treated with bilateral deep brain stimulation (DBS) GPi and STN for the treatment of Parkinson's disease (PD) were included in the study. The target was chosen by direct visual recognition of GPi and STN in three-dimensional MRI. The coordinates were automatically saved using special software and converted to the anterior commissure-posterior commissure (AC-PC) coordinate system using a matrix conversion process. The same GPi and STN targets were identified based on the locations of brain structures shown in the Schaltenbrand atlases. MRI-based GPi and STN target coordinates were statistically compared with the corresponding atlas-based coordinates.

Results: Eleven patients were included in our study. The median age was 66.6±11.72 in the GPi group and 47.50±14.20 in the STN group. The average length of the AC-PC line was 26.15±1.42 in the STN group; and 26.46±1.34 in the GPi group. It was quite similar in both groups for each coordinate measurement, and the Intra-class Correlation Coefficients of each measurement were over 90%.

Conclusion: According to the results of our study, target coordinates obtained by direct visual targeting on MRI and target coordinates obtained by indirect targeting based on atlas were highly compatible. The coordinates used for DBS in the treatment of PD were confirmed by both methods.

Keywords: MRI, deep brain stimulation, stereotactic targeting, subthalamic nucleus, globus pallidus

INTRODUCTION

Parkinsonism is a clinical syndrome that occurs with any combination of bradykinesia, resting tremor, rigidity, and postural instability. The most common form of parkinsonism is Parkinson's disease (PD); a chronic, progressive disease caused by the degenerative loss of dopaminergic neurons in the brain and characterized by clinically asymmetric parkinsonism (1). During diagnosis and treatment, many factors should be carefully evaluated, including the patient's signs, symptoms, age, stage of the disease, degree of functional disease, level of physical activity and efficiency (2). Treatment of PD can be divided into pharmacological, non-pharmacological and surgical treatment.

Deep brain stimulation (DBS) is the most commonly performed surgical procedure for the treatment of advanced PD (3). Evidence from randomized controlled trials suggests that either the DBS of the subthalamic nucleus (STN) or the internal globus pallidus (GPi) mitigate motor fluctuations and dyskinesia associated with

ORCID ID of the author: İ.S. 0000-0002-6904-6678.

Corresponding Author: İdris Sertbaş,
E-mail: idris.sertbas@yeniyuzyil.edu.tr

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advanced PD. The STN and GPi are two of the most common target structures used for DBS (3,4). The lead should be placed correctly to maximize therapeutic benefit and minimize side effects. Preoperative localization of target structures can be performed directly from stereotactic preoperative magnetic resonance imaging (MRI) or indirectly from atlas coordinates and predefined anatomical markers. Given the anatomical variability of the target core between patients and a degree of atrophy that can be found in patients with neurodegenerative diseases, the direct targeting method is unquestionably more suitable for individual patients. However, this technique can result in limited contrast and relatively low visibility of target points in standard MRI (5,6).

Technological advances in imaging methods have facilitated direct target planning and post-operative lead localization. But intraoperative verification of the electrode position relative to the intended target coordinates is difficult. Although there are very few published data documenting the best targeting method for DBS and the accuracy of any electrode placement method, there is no consensus on the subject (7-10). The aim of this study was to investigate the reliability of atlas-derived data by comparing it with direct targeting on MRI, and to assess the suitability of each technique for stereotactic targeting.

METHODS

This study was conducted in accordance with the principles of the Helsinki Declaration of the World Medical Association "Ethical Principles for Medical Research Involving Human Subjects" (held in October 2013). Ethics committee approval for this study was obtained from İstanbul Yeni Yüzyıl University Clinical Research Ethics Committee (approval number: 2020/02, date: 10.02.2020).

This study included 11 patients admitted to a neurosurgery clinic for drug-resistant PD and underwent DBS. Patients underwent bilateral electrode implantation for continuous stimulation of GPi (n=5) and STN (n=6) under local anesthesia.

Under local anesthesia, the stereotactic frame (Zamorano-Dujovny open ceramic version, Stryker Leibinger, Freiburg, Germany) was placed parallel to the anterior commissure-posterior commissure (AC-PC) line relative to the external landmarks (lower orbital ring, external auditory canal). AC-PC coordinates were determined on axial T1-weighted images (T1-WI) using MRI, Achieva 1.5 Tesla (Philips, Best, Netherlands), and the coordinates of the mid-commistatic point (AC-PC) and AC-PC distance were calculated accordingly. The location of the STN and GPi cores was found and their coordinates were calculated according to the AC-PC line. Schaltenbrand-Wahren-Atlas was also used as AC and PC reference points and merged with a volumetric T1-WI MRI data set.

The target was then chosen based on the Schaltenbrand atlas (11). In this atlas, one of the GPi and STN cores was selected, the distances between the AC and PC midpoints were measured on the Schaltenbrand atlas after the target was detected. According to the AC-PC line on the atlas; vertical, inferior and anterioposterior coordinates were determined and the plate where the DBS target was wanted to be placed was selected.

Then, in the operating room, a stereotactic electrode guidance device was mounted and a 14 mm hole was drilled at the predetermined orbital level. Microelectrode recording was not used. Electrode implantation was performed. Distal electrode tips were placed subcutaneously. Under general anesthesia, the brain pacemaker placed under the skin with iv propofol and remifentanil was connected to the electrodes. Computed Tomography was performed to control post-operative patients in terms of possible complications.

Statistical Analysis

All analyzes were done in SPSS v21 (SPSS Inc., Chicago, IL, USA). Due to the small sample size, the coordinates were analyzed with the Wilcoxon signed-ranks test. The fit of the coordinates for both methods was evaluated using Cronbach's Alpha and Intra-class Correlation Coefficient (ICC). Accordingly, we suggest that ICC values below 0 indicate "low" reliability; values between 0.5 and 0.75 indicate "moderate" reliability; values between 0.75 and 0.9 indicate "good" reliability; and values greater than 0.90 indicate "excellent" reliability (12). $P<0.05$ was considered statistically significant.

RESULTS

Eleven patients (4 females, 7 males) were included in our study. The mean age was 66.6±11.72 in the GPi group and 47.50±14.20 in the STN group.

The average length of the AC-PC line was 26.15±1.42 in the STN group. The target coordinates set in Atlas and MRI for STN showed "excellent" correlation for distances between right hemisphere dx, dz and left hemisphere dx, dy, dz (p-value for all >0.05 and ICC >0.90) (Table 1).

The average length of the AC-PC line was 26.46±1.34 in the GPi group. The target coordinates set in Atlas and MRI for GPi showed "excellent" correlation in distances between right hemisphere dx, dy, dz and left hemisphere dx, dz (p-value for all >0.05 and ICC >0.90) (Table 2).

DISCUSSION

According to the results of our study, the target coordinates we determined in Atlas and MRI for STN and GPi showed "excellent" correlation. Accordingly, DBS structures, which are often not clearly visualized using Atlas, have been verified by MRI techniques.

Reliable identification of the anatomical boundaries of STN and GPi is a critical step for DBS of these structures. Atlas-based coordinates are limited to relying only on a few brain samples, and several studies have documented inter-individual variations in the position of these nuclei. The Schaltenbrand atlas consists of successive brain slices (plates) obtained from a brain. The coordinates calculated based on the structures found in this atlas

J Acad Res Med 2020;10(3):241-5

Table 1. Distribution of STN coordinates according to patient characteristics

	Mean	SD	Median	Minimum	Maximum	p	Cronbach's Alpha	ICC
Age	47.50	14.20	47.50	31.00	69.00	-	-	-
AC-PC distance	26.15	1.42	26.30	23.80	27.60	-	-	-
Right hemisphere								
dx								
Atlas	11.82	2.13	11.15	9.70	15.90	0.109	0.995	0.992
MRI	12.08	2.29	11.50	10.00	16.50			
dy								
Atlas	2.60	2.78	1.70	0.40	8.00	0.043	0.985	0.968
MRI	3.33	2.34	2.50	2.00	8.00			
dz								
Atlas	3.67	1.36	3.80	1.40	5.00	1.000	0.992	0.993
MRI	3.67	1.51	4.00	1.00	5.00			
Left hemisphere								
dx								
Atlas	11.58	2.76	11.00	9.00	16.60	0.078	0.992	0.984
MRI	12.08	2.46	11.50	10.00	16.50			
dy								
Atlas	2.28	2.00	1.80	0.30	5.90	0.176	0.981	0.977
MRI	2.58	1.69	2.50	1.00	5.50			
dz								
Atlas	3.03	2.06	3.55	0.30	5.00	0.109	0.989	0.985
MRI	3.33	1.86	4.00	1.00	5.00			

dx, dy, and dz distances to the x, y, and z axes, respectively. p: p-values for Wilcoxon signed-ranks test, ICC: Intra-class Correlation Coefficient, SD: standard deviation, AC-PC: anterior commissure-posterior commissure, MRI: magnetic resonance imaging, STN: subthalamic nucleus

Table 2. Distribution of GPi coordinates according to patient characteristics

	Mean	SD	Median	Minimum	Max	p	Cronbach's Alpha	ICC
Age	66.60	11.72	71.00	48.00	78.00	-	-	-
AC-PC distance	26.46	1.34	26.50	25.10	28.20	-	-	-
Right hemisphere								
dx								
Atlas	17.34	2.95	15.70	15.00	22.10	0.080	0.988	0.978
MRI	18.00	2.92	17.00	16.00	23.00			
dy								
Atlas	6.56	2.76	7.90	2.20	8.90	0.223	0.991	0.990
MRI	6.80	2.68	8.00	3.00	9.00			
dz								
Atlas	2.12	1.18	1.70	1.00	3.70	0.593	0.949	0.958
MRI	2.20	1.30	2.00	1.00	4.00			
Left hemisphere								
dx								
Atlas	17.36	2.93	15.70	15.10	22.10	0.078	0.989	0.979
MRI	18.00	2.92	17.00	16.00	23.00			
dy								
Atlas	6.48	2.65	7.60	2.30	8.90	0.043	0.997	0.987
MRI	7.00	2.55	8.00	3.00	9.00			
dz								
Atlas	2.12	1.16	1.70	1.00	3.60	0.144	0.976	0.966
MRI	2.40	1.14	2.00	1.00	4.00			

dx, dy, and dz distances to the x, y, and z axes, respectively. p: p-values for Wilcoxon signed-ranks test, ICC: Intra-class Correlation Coefficient, SD: standard deviation, AC-PC: anterior commissure-posterior commissure, MRI: magnetic resonance imaging, GPi: globus pallidus internus

are not obtained from an average brain, but from a photograph that actually corresponds to a slice of a certain thickness (13). It has been recognized that the use of atlases for stereotactic neurosurgery is conditioned on data normalization according to the characteristics of each brain. However, there has been no consensus on the normalization process (14,15).

MRI allows excellent visualization of commissures, which are thalamic organization. It also shows individual anatomical variations while reducing the imaging artifacts produced by the stereotactic framework. It is possible to obtain millimeter sections with good signal with 3-D gradient-Echo reception. It allows the radiologist to position all anatomical landmarks identified by high-resolution MRI ventriculography in a non-invasive manner. In addition, structures not seen in ventriculograms, such as the internal capsule, can be visualized (16,17). There are concerns that artifacts on MRI will distract intracranial targets from their actual anatomical position, leading to errors in determining target coordinates and, as a result, failed stereotactic procedures. However, precise MRI-guided stereotactic procedures can be performed using high-field MRI with a homogeneous magnetic field and linear field gradients (18,19). In a study conducted using anatomical samples, mean stereotactic errors were reported to be 0.48±0.17 mm; 0.69±0.14 mm and 0.82±0.13 mm, respectively, in the x, y and z directions (18). Other studies that report the reliability of direct MRI coordinates are mainly based on visualizing the structure only in the coronal plane and do not target a specific subregion (20,21). In another study comparing MRI and Atlas methods for DBS in Parkinson's patients, it was concluded that high-resolution MRI, which enables direct visualization of the nucleus in both axial and coronal planes, correlates borders in both planes and creates a three-dimensional structure would be more effective (7). These results support that a functional MRI procedure can be performed safely after its accuracy has been verified by a certain stereotactic MRI standardization. A recent metaanalysis concluded that STN for DBS is difficult due to low resolution and geometric distortion in MRI sequences used in direct targeting, but that STN boundaries can be better defined with new MRI techniques. Accordingly, sensitivity-based imaging techniques and image reconstruction methods can show the way to produce high-quality, artifact-free images that neurosurgeons can use to accurately and reliably target their electrodes (22).

Study Limitations

Our study also had limitations. It is a retrospective study in nature, based on patient file records. Although the patient population is not sufficient, objective results can be obtained with prospective studies.

CONCLUSION

In light of these results, normalizing Atlas data based on the reference of more patients will bring Atlas coordinates closer to MRI targets. In addition, increased image quality along with the developing technology in the field of MRI will also allow sterotactic targeting to be performed more accurately and in a standard way. Based on the overlap of the target coordinates we determined in our study in both Atlas and MRI, we believe that the targets we determined will be a guide for subsequent studies. Randomized-controlled studies are needed on this issue.

The target coordinates we set for DBS coincide with each other in both Atlas and MRI. Due to atrophy in neurodegenerative conditions, the anatomy of patients will also be different. Therefore, a direct targeting technique based on the patient's own brain anatomy may be a more convenient way of preoperative targeting for DBS. Accurate anatomical targeting can also minimize the number of exploration marks required for physiological testing of the target, thus enabling faster and safer surgery.

Ethics Committee Approval: Ethics committee approval for this study was obtained from İstanbul Yeni Yüzyıl University Clinical Research Ethics Committee (approval number: 2020/02, date: 10.02.2020).

Informed Consent: Due to the retrospective design of the study, patient consent was not obtained.

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Comparison of COVID-19 Case-Fatality-Rates by Socio-Demographic Factors

Esra Keleş Peker[1], Güven Bektemur[2], Kürşad Nuri Baydili[3], Melek Aktaş[4]

[1]University of Health Sciences Turkey, Zeynep Kamil Training and Research Hospital, Clinic of Gynecologic Oncology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Hamidiye Faculty of Medicine, Department of Public Health, İstanbul, Turkey
[3]University of Health Sciences Turkey, Hamidiye Faculty of Medicine, Department Biostatistics and Medical Informatics, İstanbul, Turkey
[4]French School of Public Health and Political Sciences Rennes, Student master 2 in Administration of Public Health Policies and Programmes, Rennes, France

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ABSTRACT

Objective: To evaluate socio-demographic risk factors in comparison with Coronavirus disease (COVID-19) case fatality rates (CFRs).

Methods: In this cross-sectional study, we used the demographic and epidemiologic data that were identified as risk factors for COVID-19 CFRs. The electronic dataset was extracted from an open-source database, Our World in Data, and the European Center for Disease Prevention and Control websites. Countries with at least 1,000 confirmed COVID-19 cases that were reported by July 10, 2020, a reported incidence of the 14-day COVID-19 cases, and having all available parameters were included in the study. Countries with ascertained and/or missing parameters were excluded from this study. A cross-continental comparison was also performed. To analyze the data, One-Way analysis of variance (One-Way ANOVA) followed by the Bonferroni test and Pearson correlation coefficient were conducted.

Results: In the final analysis, 137 countries were eligible. The median age, population aged over 65 years, female smoking rates, and life expectancy were positively correlated with the COVID-19 CFRs, while no significant correlation was found with diabetes prevalence, frequency of available handwashing centers, and number of hospital beds per 1,000 persons. The European continent had higher COVID-19 CFRs, while the Asian continent had higher cases/1 million population.

Conclusion: It is important to highlight the risk factors for mortality due to the novel coronavirus. This will help to anticipate healthcare needs and implement appropriate mitigation strategies, as well as to prioritize the most vulnerable individuals, thereby increasing their chances of survival from COVID-19.

Keywords: Case fatality rate, COVID-19, risk factors, continents, handwashing, smoking

ORCID IDs of the authors: E.K.P. 0000-0001-8099-8883; G.B. 0000-0001-5899-566X; K.N.B. 0000-0002-2785-0406; M.A. 0000-0003-4195-5797.

Corresponding Author: Esra Keleş Peker,
E-mail: dresrakeles@hotmail.com

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INTRODUCTION

In December 2019, cases of an "unrecognized viral pneumonia" were detected among individuals working in or in contact with the local seafood market in Wuhan, China (1). The cause of this infection has been identified as a new subtype of coronavirus, referred to as Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), named Coronavirus disease (COVID-19) by the World Health Organization (WHO) (2). By the end of March 2020, the new coronavirus had spread rapidly from China to Europe, followed by a pandemic in the United States, which became the new global epicenter of the coronavirus (3,4). In early March 2020, the Director-General of the WHO declared the COVID-19 as a pandemic (5). At that time, COVID-19 had spread to six continents and all the regions of the United Nations (6).

Countries had diverse responses to the COVID-19 pandemic. Many countries have implemented national regulations, such as quarantine, curfews, travel restrictions (7), and border closings, as mitigation strategies (8). In addition, personal protective measures have been taken, including the use of face masks and hand hygiene to reduce the spread of the coronavirus.

Worldwide, the pandemic has resulted in many deaths. According to currently available data, elderly indivduals, men, and those with underlying health diseases have been more affected by this contagious infection (9,10).

The relationship between the COVID-19 infection and smoking has been examined, but remains controversial. While some studies have found an association between smoking and the disease severity and mortality, some studies have not. All of these prompted us to investigate whether there is a link between COVID-19 and smoking and whether gender plays a role in this difference.

We aimed to highlight the relationship between the socio-demographic and epidemiologic risk factors in comparison with COVID-19 case fatality rates (CFR). Furthermore, we conducted a comparison between population-based risk factors and COVID-19 CFR across the continents.

METHODS

Study Design

This cross-sectional study was conducted by examining data using the relational scanning model. The electronic dataset was extracted from the open-source database on July 10, 2020. This study was approved by the University of Health Sciences Turkey, Hamidiye Scientific Research Ethics Committee (approval number: 20/309).

Data Collection

The socio-demographic and COVID-19 data were obtained from the open-source websites, Our World in Data (https://ourworldindata.org.), and the European Center for Disease Prevention and Control websites (https://github.com/owid/covid19 data/tree/master/public/data), which are updated daily and include data on confirmed cases, deaths, and tests for all countries. The demographic and epidemiologic data that were identified as risk factors for COVID-19 CFRs were used. In the final analysis, 137 of the 215 affected countries were eligible for the study.

Abstracted data included the total number of cases per country, rate of confirmed cases per 1 million population, total population of the countries, population densities, median age, population rates over 65 and 70 years, diabetes prevalence, smoking rates among women and men, frequency of handwashing centers, number of hospital beds for 1,000 population, and life expectancy.

Study Criteria

Countries with at least 1,000 confirmed COVID-19 cases reported by July 10th, a reported incidence of the 14-day COVID-19 cases, and having all the available parameters were included in the study. Countries with ascertained and/or missing parameters were excluded from the study.

Statistical Analysis

All statistical analyses were performed using SPSS (IBM SPSS version 25) for Windows software. Percentage and frequency values for categorical variables and arithmetic mean (± standard deviation) or median values for quantitative variables were used in the descriptive statistics of the data. The relationship between CFR and all other variables were determined using the Pearson correlation coefficient. Comparisons between continents were performed using a One-Way analysis of variance (One-Way ANOVA) followed by the Bonferroni post-hoc comparison test. In this study, a type I error rate of 0.05, and p-value <0.05 were considered statistically significant.

RESULTS

We analyzed the risk factors that were identified in the socio-demographic and epidemiologic data for COVID-19 mortality. In our study, only 137 out of approximately 215 affected countries were selected for the analysis.

The total number of cases (p=0.344), rate of cases per one million population (p=0.501), total population of the country (p=0.513), population density (p=0.252), diabetes prevalence (p=0.097), smoking rates among men (p=0.641), frequency of available hand washing centers (p=0.495), number of hospital beds per 1,000 population (p=0.395), and mortality rates were not significantly correlated with COVID-19 CFRs. Median age (p=0.001; r=0.272), population aged >65 years (p<0.001; r=0.366), population aged >70 years (p<0.001; r=0.378), and female smoking rate (p<0.001; r=0.301) were positively correlated with COVID-19 CFR. A very weak positive correlation was found between life expectancy (p=0.011; r=0.219) and COVID-19 CFR (Table 1).

A significant difference was determined between the COVID-19 CFRs and cases/one million (p=0.005), deaths/one million (p<0.001). The continents of Asia and South America in cases/one million and Europe and South America in deaths/one million had higher values than other continents. The European continent had the highest COVID-19 CFR value (Table 2). In addition, the case fatality rates of the countries participating in our study are shown in Figure 1.

Table 1. Socio-demographic risk factors and COVID-19 case fatality rates

		Case fatality rates
Total cases	r	0.081
	p	0.344
	N	137
Total cases (per million)	r	-0.058
	p	0.501
	N	137
Population	r	0.056
	p	0.513
	N	137
Population density (people per sq. km of land area)	r	-0.099
	p	0.252
	N	136
Median age	r	0.272
	p	**0.001**
	N	136
Aged >65 years (% percent)	r	0.366
	p	**<0.001**
	N	136
Aged >70 years (% percent)	r	0.378
	p	<0.001
	N	135
Diabetes prevalence (% of population ages 20 to 79)	r	-0.143
	p	0.097
	N	136
Female smokers (% of adults)	r	0.301
	p	**0.001**
	N	111
Male smokers (% of adults)	r	-0.045
	p	0.641
	N	109
Handwashing facilities (% percent)	r	0.087
	p	0.495
	N	64
Hospital beds (per 1,000 population)	r	0.077
	p	0.395
	N	123
Life expectancy	r	0.219
	p	**0.011**
	N	136

*p<0.05. COVID-19: Coronavirus disease

J Acad Res Med 2020;10(3):246-51

DISCUSSION

In this study, we investigated the risk factors of the COVID-19 CFR according to demographic and epidemiologic characteristics. In reported studies to date, several risk factors have been associated with the disease mortality. The most important factors affecting the fatality rates were demographic characteristics such as age, smoking, and underlying health conditions (9,11,12). This study revealed that age over 65 years and longer life expectancy were significantly correlated with increased mortality among COVID-19 patients across countries, which is consistent with most published data to date (13-15). This is explained by the fact that, as individuals age, they have concomitant diseases that could weaken their immune system, making them vulnerable to this disease (14,16). This finding suggests that protective measures against COVID-19 should be implemented, especially in places such as nursing homes.

Figure 1. Case fatality rates of COVID-19 pandemic, July 10, 2020

CFR: Case fatality rates, COVID-19: Coronavirus disease

Remuzzi and Remuzzi (17) indicated that the mean age of patients who died from COVID-19 in Italy was 81 years, and two-thirds of them had underlying health conditions such as diabetes or were smokers. Since Italy is the country with one of the longest life expectancies and has an elderly population in Europe, it had the majority (77.4%) of COVID-19 cases reported from Europe as of February 29 (6). As a result, Italy was the top affected country in Europe, followed by Spain, France, and Germany, and had the highest COVID-19 case-fatality rates in Europe. Consequently, these explain why the COVID-19 CFR of Europe was higher compared to that of other continents. This fact differs in China, which makes up only 12% of the elderly population in the Asian continent, explaining why the Asian continent lagged behind in the continental ranking in terms of deaths/one million population.

In the cross-continental comparison of cases and deaths per one million population, continental rankings have changed. Several reasons for this change include the differences in the socio-demographic structures between countries, such as age, life expectancy, population density, and accompanying diseases.

While the COVID-19 CFR is expected to be high in impoverished continents such as Africa, due to insufficient protective equipment, poor sources, and low number of physicians per

Table 2. Comparison of total cases, deaths, and CFRs between continents

	Continents	Mean	SD	F	p
Total cases/1 M (per million)	Africa	724.69	1134.95	3.846	**0.005**
	Asia	3921.72	6925.53		
	Europe	2747.82	2048.63		
	North America	3007.26	3120.68		
	South America	5182.69	5174.95		
Total deaths/1 M (per million)	Africa	11.93	15.30	9.396	**<0.001**
	Asia	31.0	40.67		
	Europe	163.79	212.57		
	North America	109.90	123.82		
	South America	174.94	149.38		
Case fatality rate	Africa	2.31	1.67	4.616	**0.002**
	Asia	2.42	4.47		
	Europe	5.43	4.52		
	North America	3.75	3.07		
	South America	3.13	2.07		

*p<0.05. CFR: case fatality rate, SD: standard deviation

capita, we are facing low CFR results. Additionally, although the number of cases is high in India, the reported death rates are low. The reasons for the different or unreliable CFR results between countries that make it difficult to compare the CFRs can be listed as follows: definition of death due to COVID-19 varies between countries, different ways of measuring CFRs, insufficient number of tests, differences in the timing of tests and tracing the contacts, shortages of personal protective equipment, inadequate number of available intensive care beds, presence of different health systems, and political factors.

To our knowledge, no previous study has shown that diabetes has an independent predictive value for mortality, but a large number of studies have been conducted on the impact of diabetes on the disease progression and prognosis of COVID-19 patients (10). In addition, we have not found an association between diabetes prevalence and COVID-19 CFR.

Researchers have investigated smoking as one of the epidemiologic risk factors for COVID-19 disease (15,18), but it is still controversial. In a meta-analysis, a statistically significant association was found between the risk of severe COVID-19 disease and death among smokers (19,20). In the study of Zhang et al. (13), only 1.4% of patients were smokers, while in the study of Guan et al. (21), the rate of smokers was 12.6%. When comparing the ratio of a small number of smokers to the proportion of smokers in the world, we are unable to draw a definitive relationship between the incidence or severity of COVID-19 and smoking status due to the lack of data (22). In our study, when we analyzed the association between smoking status and the COVID-19 CFRs in terms of gender, women smokers were more likely than men smokers to die of the coronavirus. Data from 137 countries suggest that this may be explained by the longer life expectancy of women compared to men. Even though these results differ from some earlier studies, compared with what was previously known, we currently do not have sufficient evidence to take into consideration the gender roles between smokers and the COVID-19 CFRs. To date, there is no convincing evidence demonstrating that hand hygiene can reduce the spread of SARS-CoV-2 (23). Although handwashing plays a crucial protective role in deterring epidemic transmission, the significance of reducing the spread of COVID-19 infection is effective when combined with strategies that include simple preventative measures such as face mask use, disinfection, social distancing, and disease awareness rather than only emphasizing the importance of hand hygiene (24). Our study results are also in line with previous studies.

Study Limitations

The strength of our study is that it covers countries with over 1,000 reported COVID-19 cases, which enables stable analysis. However, this study has several limitations. The first is that the epidemiologic data was collected using a retrospective design. The second is the under-reporting or lack of additional information, such as medications, body mass index, behavioral changes, and gender-checked smoking status, all of which may influence the published results. Hence, we recommend further detailed research to highlight these knowledge gaps regarding the COVID-19 pandemic.

CONCLUSION

In summary, this article highlighted the risk factors affecting COVID-19 CFRs across countries, which will help to determine appropriate mitigation strategies, prioritize the most vulnerable individuals, and increase their chances of survival from the COVID-19.

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Hamidiye Scientific Research Ethics Committee (approval number: 20/309).

Informed Consent: Cross-sectional study.

Peer-review: Externally peer-reviewed.

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J Acad Res Med 2020;10(3):246-51

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Relationship Between Vitamin D, Calcium, and Phosphorus Levels

Burcu Çaykara[1], Güler Öztürk[1], Hacer Hicran Mutlu[2], Ebru Arslan[1]

[1]İstanbul Medeniyet University Faculty of Medicine, Department of Physiology, İstanbul, Turkey
[2]İstanbul Medeniyet University Faculty of Medicine, Department of Family Medicine, İstanbul, Turkey

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ABSTRACT

Objective: Our study aimed to determine the relationship between the prevalence of vitamin D deficiency and calcium and phosphorus levels by retrospectively obtaining vitamin D, calcium, and phosphorus values.

Methods: Vitamin D, calcium, and phosphorus levels of patients admitted to family medicine between October 2015 and December 2017 were evaluated. Shapiro-Wilk, Mann-Whitney U, and Spearman's rho tests were used for data analysis and p-values <0.05 were considered to be statistically significant.

Results: A total of 1,063 patients were included in the study. The percentage of patients with normal vitamin D levels was 20.5% and those with normal calcium and phosphorus levels were 97.1% and 84.9% of the study population, respectively. Positive correlation was found between vitamin D levels, calcium, and age.

Conclusion: In our study, the prevalence of vitamin D deficiency was found to be 49.6%.

Keywords: Vitamin D, calcium, phosphorus

INTRODUCTION

Vitamin D is synthesized in the skin by exposure to sunlight, but can also be obtained exogenously from the diet (1). Dehydrocholesterol in the skin is converted to previtamin D by exposure to sunlight. Previtamin D is transported to the liver where it is converted into 25-hydroxyvitamin D [25(OH)D], which is the major circulating form. 25(OH)D is further converted in the kidney into the active form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] (2). To assess vitamin D levels, measurement of serum 25(OH) D, which has a half-life of about three weeks is performed (3). Vitamin D, which is fat soluble, plays an important role not only in the musculoskeletal system, but also in all tissues, which have vitamin D receptors (4). The main function of vitamin D is to maintain calcium (Ca) and phosphorus (P) balance in the body by promoting Ca and P absorption from the intestines and kidneys (5). In vitamin D deficiency, only 10%-15% of calcium and 50%-60% of phosphorus can be absorbed from ingested foods (6).

Serum 25(OH)D levels are interpreted as follows; <10 ng/mL-severe deficiency, <20 ng/mL-deficiency, 20-30 ng/mL-insufficiency, >30 ng/mL-sufficient, and >150 ng/mL-intoxication (7,8). It is reported that the main underlying cause of vitamin D deficiency, which is now considered to be a global health issue, is insufficient

ORCID IDs of the authors: B.Ç. 0000-0001-7063-2140; G.Ö. 0000-0001-6556-3662; H.H.M. 0000-0003-3712-0068; E.A. 0000-0001-5309-3931.

Corresponding Author: Burcu Çaykara,
E-mail: burcu.caykara@medeniyet.edu.tr

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exposure to sunlight (9). Vitamin D levels can also be affected by other factors such as age, sex, ethnicity, and seasonal variations (10). Low levels of vitamin D were found to be associated with hypertension, cardiovascular diseases, chronic musculoskeletal pain, and various malignancies (4). Our study aimed to determine the relationship between vitamin D deficiency and calcium and phosphorus levels.

METHODS

Vitamin D, calcium, and phosphorus levels from the hospital registries of İstanbul Medeniyet University, Göztepe Training and Research Hospital, Department of Family Medicine between October 2015 and December 2017 were retrospectively evaluated. Ethical approval was obtained from the Ethics Committee of İstanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 2018/0336, date: 12.09.2018). Since our study was retrospective, consent forms were not obtained from patients. All subjects who had been tested concurrently for vitamin D, calcium, and phosphorus levels were included in the study. In cases where there was more than one measurement of the subjects under follow-up, the date of the first measurement was taken into consideration, and other measurements of the same subject were not included in the study.

Statistical Analysis

SPSS 22 (IBM Corp.; Armonk, NY, USA) were used for statistical analysis. Data analyses were performed with Shapiro-Wilk, Mann-Whitney U and Spearman's rho tests. P-value <0.05 was considered to be statistically significant.

RESULTS

The number of subjects who had undergone concurrent measurements of vitamin D, calcium, and phosphorus levels between October 2015 and December 2017 was determined to be 1,063, of which 298 were male and 765 were female. The mean age of the subjects admitted to the department of family medicine was 50.48±17.51, the mean vitamin D value was 22.24±14.85, the mean calcium value was 9.45±0.46, and the mean phosphorus value was 3.64±0.56. When these values were compared between men and women, it was determined that only phosphorus values in women were statistically significantly higher than men (Table 1). The vitamin D levels of the 1,063 subjects were as follows: 198 (18.6%) were at or below 10 ng/mL, 329 (31%) were between 10 ng/mL and 20 ng/mL, 317 (29.8%) were between 20 ng/mL and 30 ng/mL, 218 (20.5%) were between 30 ng/mL and 150 ng/mL, and only one subject had a vitamin D level (0.1%) above 150 ng/mL (Table 2). Vitamin D levels were similar between women and men. When grouped according to vitamin D levels, a statistically significant difference was found between men and women only at levels of 30 ng/mL and 150 ng/mL (p=0.019) (Table 3). Based on calcium levels, subjects were divided into hypocalcemia, normal, and hypercalcemia groups; 13 (1.2%) subjects had hypocalcemia, 18 (1.7%) subjects had hypercalcemia, and 1,032 (97.1%) subjects

Table 1. The mean values of patient data

Category	Number	Minimum	Maximum			Mean			SD		
Age (year)	1,063	3	94			50.48			17.51		
Vitamin D (ng/mL)	1,063	2.6	150.8			22.24			14.85		
Calcium (mg/dL)	1,063	5.9	11.7			9.45			0.46		
Phosphorus (mg/dL)	1,063	1.80	6.8			3.64			0.56		
Men						**Women**					
Category	**Number**	**Minimum**	**Maximum**	**Mean**	**SD**	**Number**	**Minimum**	**Maximum**	**Mean**	**SD**	**p**
Age (year)	298	3	93	51.57	18.69	765	4	94	50.05	17.02	0.109
Vitamin D (ng/mL)	298	5.1	89.2	22.22	11.54	765	2.6	150.8	22.25	15.96	0.086
Calcium (mg/dL)	298	7.2	11.1	9.48	0.43	765	5.9	11.7	9.44	0.47	0.239
Phosphorus (mg/dL)	298	2	6.1	3.49	0.59	765	1.8	6.8	3.7	0.54	<0.001

SD: standard deviation

Table 2. Serum 25(OH)D values

n=1,063	Minimum	Maximum	Mean	SD
	2.6	150.8	22.24	14.85
	n		%	
<10 ng/mL	198		18.6	
10-20 ng/mL	329		31	
20-30 ng/mL	317		29.8	
30-150 ng/mL	218		20.5	
>150 ng/mL	1		0.1	

SD: standard deviation, 25(OH)D:

had normal calcium levels (Table 4). When calcium levels were compared based on gender, no significant difference was observed between men and women (Table 5). Based on phosphorus levels, subjects were divided into hypophosphatemia, normal, and hyperphosphatemia groups; 98 (9.2%) subjects had hypophosphatemia, 63 (5.9%) subjects had hyperphosphatemia, and 902 (84.9%) subjects had normal phosphorus levels (Table 6). When phosphorus levels were compared based on gender, phosphorus levels were found to be significantly higher in women compared to men. Furthermore, a significantly higher number of women (87.2%) were in the normal phosphorus level group (3-4.5 mg/dL) compared to men (78.9%) (p<0.001) (Table 7). Spearman's rho test showed that vitamin D levels were positively correlated with calcium and age (p<0.001) (Table 8).

Table 3. Serum 25(OH)D values to gender

Men					**Women**					
n=298	**Minimum**	**Maximum**	**Mean**	**SD**	**n=765**	**Minimum**	**Maximum**	**Mean**	**SD**	**p**
	5.1	**89.2**	**22.22**	**11.54**		**2.6**	**150.8**	**22.25**	**15.96**	**0.086**
	n		%			n		%		p
<10 ng/mL	36		12.1		<10 ng/mL	162		21.2		0.064
10-20 ng/mL	106		35.6		10-20 ng/mL	223		29.2		0.25
20-30 ng/mL	96		32.2		20-30 ng/mL	221		28.9		0.413
30-150 ng/mL	60		20.1		30-150 ng/mL	158		20.7		0.019
>150 ng/mL	0		0		>150 ng/mL	1		0.1		-

SD: standard deviation, 25(OH)D: 25-hydroxyvitamin D

Table 4. Calcium values

n=1,063	**Minimum**	**Maximum**	**Mean**	**SD**
	5.9	**11.7**	**9.45**	**0.46**
	n		**%**	
Hypocalcemia <8.5 mg/dL	13		1.2	
Normal 8.5-10.5 mg/dL	1032		97.1	
Hypercalcemia >10.5 mg/dL	18		1.7	

SD: standard deviation

Table 5. Calcium values to gender

Men					**Women**					
n=298	**Minimum**	**Maximum**	**Mean**	**SD**	**n=765**	**Minimum**	**Maximum**	**Mean**	**SD**	**p**
	7.2	**11.1**	**9.48**	**0.43**		**5.90**	**11.7**	**9.44**	**0.47**	**0.239**
	n		**%**			**n**		**%**		**p**
<8.5 mg/dL	1		0.3		<8.5 mg/dL	12		1.6		0.276
8.5-10.5 mg/dL	292		98		8.5-10.5 mg/dL	740		96.7		0.36
>10.5 mg/dL	5		1.7		>10.5 mg/dL	13		1.7		0.424

SD: standard deviation

Table 6. Phosphorus values

n=1,063	**Minimum**	**Maximum**	**Mean**	**SD**
	1.8	**6.8**	**3.64**	**0.56**
	n		%	
Hypophosphatemia <3 mg/dL	98		9.2	
Normal 3-4.5 mg/dL	902		84.9	
Hyperphosphatemia >4.5 mg/dL	63		5.9	

SD: standard deviation

J Acad Res Med 2020;10(3):252-7

Table 7. Phosphorus values to gender

Men					Women					
n=298	Minimum	Maximum	Mean	SD	n=765	Minimum	Maximum	Mean	SD	p
	2	6.1	3.49	0.59		1.8	6.8	3.7	0.54	<0.001
	n		%			n		%		p
<3 mg/dL	49		16.4		<3 mg/dL	49		6.4		0.813
3-4.5 mg/dL	235		78.9		3-4.5 mg/dL	667		87.2		<0.001
>4.5 mg/dL	14		4.7		>4.5 mg/dL	49		6.4		0.174

SD: standard deviation

Table 8. The correlation analysis for vitamin D, phosphorus, calcium, age, and gender

		Vitamin D	Phosphorus	Calcium	Age	Gender
Vitamin D	Correlation coefficient	1.00	0.016	0.125	0.303	0.053
	p-value	-	0.602	**<0.001****	**<0.001****	0.086
Phosphorus	Correlation coefficient	0.016	1.00	0.009	-0.068	-0.202
	p-value	0.602	-	0.777	0.026*	**<0.001****
Calcium	Correlation coefficient	0.125	0.009	1.00	0.078	0.036
	p-value	**<0.001****	0.777	-	**0.011***	0.239
Age	Correlation coefficient	0.303	-0.068	0.078	1.00	0.049
	p-value	**<0.001****	**0.026***	0.011*	-	0.109
Gender	Correlation coefficient	0.053	-0.202	0.036	0.049	1.00
	p-value	0.086	**<0.001****	0.239	0.109	-

*p<0.05, **p<0.001

DISCUSSION

The present study shows that the prevalence of vitamin D deficiency and insufficiency were 49.6% and 29.8%, respectively, in our study population. The proportions of subjects with normal calcium and phosphorus levels were 97.1% and 84.9%, respectively. Furthermore, vitamin D levels were found to positively correlate with calcium and age (p<0.001).

Vitamin D plays an important role in cellular growth and proliferation, homeostasis, oxidative stress and cellular transport (11). Vitamin D enhances calcium absorption in the intestine to maintain adequate serum calcium concentrations and is essential for bone growth and remodeling by osteoblasts and osteoclasts. A meta-analysis study found that synergistic administration of calcium and vitamin D could reduce general bone fractures by 15% and hip fractures by 30% (12). A study conducted in Spain reported that daily dietary intake of calcium and vitamin D alone was not sufficient to maintain adequate serum levels (13). Factors such as decreased vitamin D absorption, low vitamin D intake and little or no sun exposure, obesity, and darker skin pigmentation may increase risk of vitamin D deficiency, which is currently considered to be a global pandemic (14,15).

The prevalence of vitamin D deficiency was found to be 75.2% in northwestern China, and the predictors of vitamin D deficiency included dyslipidemia, coronary heart disease, obesity, smoking, age, and sex (16). Another study in the United Kingdom showed that 61.5% of the study population was vitamin D deficient, and low socio-economic status, high body mass index, and cold season were associated with low vitamin D levels (17). The prevalence of vitamin D deficiency was found to be 87.1% in urban residents in Beijing and highly prevalent during the winter and spring seasons (18). Although one study found that vitamin D inadequacy and deficiency increased the odds of diabetes two-fold (19), another study conducted in Turkey found no difference between type 1 diabetics and healthy controls (20).

Yu et al. (21) found that 5.9%, 50%, and 38.7% of the study population were severely vitamin D deficient (<10 ng/mL), vitamin D deficient (10-20 ng/mL), and vitamin D insufficient (20-30 ng/mL), respectively. Only 5.4% of the participants were vitamin D sufficient (>30 ng/mL) and vitamin D deficiency was found to be higher in women (66.3%) compared to men (45.3%, p<0.01) (21). In our study, we found vitamin D levels of 198 subjects (18.6%) to be below 10 ng/mL, 329 subjects (31%) to be between 10-20 ng/mL, 317 subjects (29.8%) to be between 20-30 ng/mL, 218 subjects (20.5%) to be between 30-150 ng/mL, and only one subject (0.1%) had a vitamin D level ≥150 ng/mL.

In a study conducted in Saudi Arabia, vitamin D deficiency and insufficiency were found in 50% and 43.8%, respectively, among 160 pregnant women (22). Vitamin D deficiency was found in

about 44.6% of pregnant Turkish women in İzmir, which is a city in the Aegean region of Turkey (23). Another study found that 97.8% of pregnant women belonging to low socio-economic status were vitamin D deficient. 25(OH)D levels of maternal serum and cord blood were found to positively correlate. The findings of that study suggested that vitamin D stores of the mother directly affect neonatal vitamin D status (24). Öztürk et al. (25) found that 94.92% of participants had serum vitamin D levels <30 ng/mL and 75.54% of the participants were vitamin D deficient in Gaziantep, another city located in the southeastern province of Turkey. When vitamin D levels were compared between men and women, no significant difference was found in our study. We found that 79.4% of our study population had serum vitamin D levels below 30 ng/mL. Similarly, a study conducted in Oman found that 79% of the study population had vitamin D levels below 30 ng/mL and the study population had normal serum calcium and alkaline phosphatase levels (26). Furthermore, 80.3% of the study population were found to have levels <30 ng/mL in a study conducted in northern France, and 25(OH)D levels were found to correlate positively with $1,25(OH)_2D$ and negatively with parathyroid hormone, but did not correlate with serum calcium or phosphate levels (27). We observed that 97.1% and 84.9% of our study population had normal calcium and normal phosphorus levels, respectively. When phosphorus levels were compared based on gender, it was found to be significantly higher in women compared to men. Furthermore, a significantly higher proportion of women (87.2%) were in the normal phosphorus (3-4.5 mg/dL) level group ($p<0.001$) compared to men (78.9%). We found that vitamin D levels were positively correlated with calcium and age but not with phosphorus levels.

Vitamin D deficiency was found in 73.9% of Turkish patients suffering from widespread musculoskeletal pain, and factors associated with hypovitaminosis included sex, age, and season (especially March) (28). A total of 75.2% of female and 33.7% male medical faculty students had vitamin D levels <20 ng/ml in Malatya (29). In our previous study, it was reported that 75% of the participants had levels <20 ng/mL, 16.1% had levels between 20-30 ng/mL, and 8.9% had levels ≥30 ng/mL (30). In the current study, we found sufficient vitamin D levels (≥30 ng/mL) in 20.5% of the study population (different study population and different timeline). Although our current as well as previous studies included subjects living in the Marmara region, the differing results may be due to the regular follow-up of the current subject group in a single department and more conscious practices to prevent vitamin D deficiency.

Study Limitations

The limitations of our study include not knowing the underlying disease condition of the subjects, absence of age restriction while selecting the participants, addition of triple test (vitamin D, calcium, phosphorus) for the first time, not including subjects who had these same tests before October 2015, and including only subjects who applied to the department.

CONCLUSION

Our study showed that prevalence of vitamin D deficiency is high in the Turkish population despite Turkey being a sunny country and presence of awareness about vitamin D deficiency among the population. Our study population generally had normal calcium and phosphorus levels.

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of İstanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 2018/0336, date: 12.09.2018).

Informed Consent: Since our study was retrospective, consent forms were not obtained from patients.

Peer-review: Externally peer-reviewed.

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Association of Attention Deficit Hyperactivity Disorder Symptoms of Parents with Parental Attitudes

Mehmet Çolak[1], Özlem Şireli Bingöl[2], Zeynep Esenkaya Usta[3], Birim Günay Kılıç[4]

[1]Self-Employed Physician, Child and Adolescent Mental Health and Diseases, İzmir, Turkey
[2]Self-Employed Physician, Child and Adolescent Mental Health and Diseases, Muğla, Turkey
[3]Konya Training and Research Hospital, Clinic of Child and Adolescent Mental Health and Diseases, Konya, Turkey
[4]Ankara University Faculty of Medicine, Department of Child and Adolescent Mental Health and Medicine, Ankara, Turkey

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ABSTRACT

Objective: The aim of this study was to examine the relationship between the level of attention deficit hyperactivity disorder (ADHD) symptoms and the attitudes of parents of children diagnosed with ADHD.

Methods: According to the Diagnostic and Numerical Manual of Mental Disorders-IV diagnostic criteria, 66 children with an age range of 6-13 were diagnosed with ADHD and their parents who brought them to the interview. A total of 94 parents were included in the study, including both the mother and father of some children diagnosed with ADHD, the mother of some, and the father of some. Parents of the children were evaluated with the "Wender-Utah Rating Scale (WURS)", "Parenting Styles and Dimensions Scale (PSDS-SF)".

Results: According to the results of our study; it was found that the permissive subscale scores of PSDS-SF were significantly higher in parents whose WURS scores were above the cut-off value compared to those whose WURS scores were below the cut-off value, and there was no significant difference between the two groups in terms of competent and authoritarian subscale scores of PSDS-SF. It was found that there was no significant association between parents' age and educational levels and their parent's attitudes. In addition, comparisons of parents in terms of ADHD symptom level and parental attitudes did not show significant differences between parents in terms of both variables.

Conclusion: The results of our study showed that permissive attitudes were significantly higher in parents with high levels of ADHD symptoms. In a clinical approach to children diagnosed with ADHD, it is believed that evaluating the symptoms and attitudes of parents with ADHD and psychoeducation of parents about adult ADHD are important for treatment.

Keywords: ADHD, adult ADHD, parental attitudes

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is defined as a neurodevelopmental disorder characterized by decreased sustained attention, increased impulsivity, and/or mobility. It is quite common in children and adolescents and has been shown to have an average worldwide prevalence of 5.9-7.1% (1). ADHD, which begins in childhood, also persists in the adult period at a rate of 50-70% (2,3).

ADHD is a genetic transitive disorder, and the incidence of ADHD in the mothers and/or fathers of children with ADHD is high

ORCID IDs of the authors: M.Ç. 0000-0003-4880-3892; Ö.Ş.B. 0000-0002-5549-4154; Z.E.U. 0000-0003-0925-7868; B.G.K. 0000-0002-4566-2564.

Corresponding Author: Özlem Şireli Bingöl,
E-mail: ozlemsireli@gmail.com

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compared to the healthy population. In Turkey, in 2005, a cross-sectional study evaluating the parents of 69 ADHD diagnosed and monitored children found that 33.8% of parents met ADHD diagnostic criteria (4). Another recent study in Turkey evaluated 135 children with ADHD and 135 control groups and found that the level of ADHD symptoms of parents of children with ADHD was significantly higher than that of the control group (5). Overall, the lifetime prevalence of ADHD in adults is known to be 1.1-5% (6,7). Lifelong clinical features of ADHD are manifested in different forms in adults. Inattention causes symptoms in individuals such as forgetfulness, contemplation, inability to listen, difficulty in making decisions, lack of planning skills, inability to use time properly, failures in performing tasks, postponement or inability to finish work. While hyperactivity causes symptoms such as inner restlessness, tension, talking too much, not being able to sit for a long time; impulsivity causes symptoms such as taking action without thinking, inability to wait in line, constant attention seeking, frequent job and traffic accidents, frequent job and partner changes, and inappropriate sexual experiences (8). Adult ADHD, where the rate of co-diagnosis is also high, negatively affects people's relationships, work and family life (9,10).

In general, the attitude of parents is defined as the whole of the attitudes and behaviors that parents display in their relationship with the child. Researchers evaluated parental attitudes in many dimensions, such as control, control, temperature, showing the necessary attention, open communication, and defined different classifications. Baumrind (11) defined three basic parenting attitudes as "democratic/balanced (authoritative)", "authoritarian (authoritarian)" and "permitting". In Democratic parental attitudes, open communication with the child and the necessary emotional support are provided; appropriate conditions are provided for the child to develop autonomy by keeping the child's behavior under supervision within a certain discipline. In authoritarian (authoritarian) parental attitudes, parents have a strict understanding of discipline, the child is not shown sufficient emotional support and warmth. In permissive parental attitudes, there is a weakness in controlling and controlling the child's behavior (11). According to the results of the research, while accepted democratic parental attitudes have positive effects on the development of the child, authoritarian and permissive attitudes have negative effects on many areas such as the child's self-development, emotion regulation and social adaptation (12).

In studies that examined the attitudes of parents, it was found that the parenting skills and attitudes of parents of adults with ADHD were negatively affected (13). A study conducted with 147 ADHD, 107 healthy children and their mothers to assess the relationship of mothers with ADHD diagnoses and attitudes found that mothers diagnosed with ADHD exhibit negative attitudes more often than other mothers, and have difficulty practicing consistent and effective discipline (14).

In another study conducted with 90 parents diagnosed with ADHD and 120 healthy groups in which parental attitudes were examined; it has been determined that parents with ADHD display more authoritarian attitudes and behave overly reactively than healthy parents, while parents in the control group have more permissive attitudes (15).

Although ADHD is a neurodevelopmental disorder, psychosocial factors such as parental attitudes are known to be important in terms of ADHD symptom severity and prognosis (16,17). There are many studies in Turkey that assess parental attitudes in children with ADHD (18-25). However, there are limited studies evaluating the parental attitudes and parents in terms of ADHD symptoms in children with ADHD (26). The aim of this study is; to examine the relationship between the ADHD symptom level of parents of children diagnosed with ADHD and parental attitudes.

METHODS

Sample

In this study, 66 children who applied to Ankara University Faculty of Medicine, Department of Child and Adolescent Psychiatry Outpatient between March 2012 and August 2012, were diagnosed with ADHD according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria, and their parents who brought them to the interview were included. A total of 94 parents, some of them both mothers and fathers, some only mothers and some only fathers of children with ADHD were included in the study. The presence of any chronic medical disease other than ADHD in children, concomitant diffuse developmental disorder, psychotic disorder, mental retardation (IQ lower than 80), and the presence of any chronic medical disease in parents were determined as exclusion criteria. In the study, the minimum sample width required to obtain 80% power ($1-\beta=0.80$) at the nominal meaning level of $\alpha=0.05$ was determined as n=94 versus the effect size of r=0.3.

Data Collection Tools

Sociodemographic data form: This form prepared by researchers questions demographic information such as age of children, gender, age of parents, level of education.

Wender-Utah Rating Scale: This scale developed by Ward and Wender (1993); evaluates the presence and severity of childhood ADHD symptoms in adults. Its Turkish validity and reliability study was conducted by Öncü et al. (27). Wender-Utah Rating Scale (WURS) is a 5-point Likert type self-report scale consisting of 25 items. Each item is rated between 0 and 4 and the cut-off score of the scale is determined as 36. Sensitivity was 82.5% and specificity was 90.8% when the breakpoint was taken 36 and above.

Parenting Styles and Dimensions Scale: This scale developed by Robinson et al.; evaluates the attitudes of parents with children between the ages of 3-13. Turkish validity and reliability studies of the scale were carried out by Kapçı and Erdinç (28). Parenting Styles and Dimensions Scale (PSDS-SF) consists of 32 items and is a 5-point Likert type self-report scale. Parents' attitudes are evaluated in three dimensions as "authoritative", "authoritarian" and "permissive". In reliability analysis, the Cronbach Alpha Coefficient was calculated as 0.88 for the competent subscale,

0.74 for the competent subscale, and 0.64 for the permitting subscale. The test-retest reliability coefficient of the scale is 0.64.

Process

The children and their parents in the study group were informed about the purpose and method of the study and their written consents were obtained. WURS and PSDS-SF scales were applied to the parents of children diagnosed with ADHD according to DSM-IV-TR.

Statistical Analysis

All data were evaluated using the SPSS Windows version 24.0 software. "Shapiro-Wilk test" and "Levene's test" were used for the suitability of the homogeneous variance assumption for the analysis of the suitability of the data for the normal distribution. In comparison of continuous variables, the "Student's t-test" was used when parametric assumptions were met, and the "Mann-Withney U test" when parametric assumptions were not met. Relations of continuous variables were evaluated by the "Pearson correlation test" and relations of discrete and sequential variables were evaluated by the "Spearman Rho correlation test". P-value of <0.05 was considered statistically significant.

RESULTS

Of the children enrolled in the study, 14 (21.2%) were girls, 52 (78.8%) were boys, and the average age was 9.83±2.42 years. Of the 94 parents included in the study, 54 (57.4%) were mothers and 40 (42.6%) were fathers. The mean age of the mothers was found to be 35.74±4.89 years, and the average age of the fathers as 39.28±6.63 years. When the education levels of the parents are evaluated; 3 of the mothers (5.6%) were only literate, 17 (31.5%) were primary school graduates, 12 (22.2%) were secondary school, 17 (31.5%) were high school, 1 (1.9%) were high school, 4 of them (7.4%) were university graduates; 14 of the fathers (35%) primary school, 5 (12.5%) secondary school, 13 (32.5%) high school, 2 (5%) college graduates, 6 (15%) of them are university graduates.

When the WURS scores of the parents were evaluated, it was determined that 12 (12.7%) of the WURS scores were above the cut-off score (36). When the parents' WURS scores were divided into two groups according to their cut-off scores and evaluated in terms of PSDS-SF scores; it was determined that the permissive subscale score of PSDS-SF was significantly higher in the parents whose WURS score was above the cut-off score compared to the parents whose WURS score was below the cut-off score (p=0.04) (Table 1).

When the parents' scale scores were evaluated separately as parents, there was no statistically significant difference between the parents' WURS and PSDS-SF scores (p>0.05) (Table 2).

When the relationship between the age and education levels of mothers and fathers and PSDS-SF scores were examined; There was no significant relationship between age and education levels and PSDS-SF scores (p>0.05) (Table 3).

Table 1. Assessment of parents' PSDS-SF scores based on WURS cut-off scores

	WURS >36 (mean ± SD)	WURS <36 (mean ± SD)	p
PSDS-SF			
Competent	57.08±12.10	56.68±11.38	0.82
Authoritarian	25.58±6.06	23.99±6.86	0.38
Permissive	15.17±3.71	12.84±3.48	0.04*

*p<0.05; Mann-Whitney U test, PSDS-SF: Parental Styles and Sizes Scale, WURS: Wender-Utah Rating Scale, SD: standard deviation

Table 2. Assessment of parents in terms of WURS, PSDS-SF scores

		Mother (n=54) (mean ± SD)	Father (n=40) (mean ± SD)	p
WURS		18.69±12.08	22.43±14.76	0.18
PSDS-SF	Competent	58.07±11.48	54.93±11.21	0.18
	Authoritarian	24.26±6.67	24.10±6.95	0.91
	Permissive	13.48±3.66	12.67±3.44	0.28

Student's t-test; PSDS-SF: Parental Styles and Sizes Scale; WURS: Wender-Utah Rating Scale, SD: standard deviation

Table 3. Relationship between age and education levels of parents and PSDS-SF scores

	PSDS-SF					
	Competent		Authoritarian		Permissive	
	r	p	r	p	r	p
Age	-0.094	0.36	0.017	0.86	0.009	0.93
Education level	0.071	0.49	-0.061	0.55	0.001	0.99

Pearson correlation test, Spearman Rho correlation test, PSDS-SF: Parental Styles and Sizes Scale

J Acad Res Med 2020;10(3):258-63

DISCUSSION

According to the results of our study; parents with high ADHD symptom levels were found to have significantly higher permissive parental attitudes than parents with low ADHD symptoms, and there was no significant difference between the two groups in terms of competent and authoritarian attitudes. No significant association was found between parental attitudes and the age and educational level of parents. In addition, comparisons of parents in terms of ADHD symptom level and parental attitudes did not show significant differences between parents in terms of both variables.

Studies show that parents with ADHD are associated with signs and symptoms of ADHD and negative parental attitudes. Forty-four months of age with an average of 258 children and their parents with a 3-year longitudinal study, mothers' levels of ADHD and ADHD symptoms in children examined early and late-term relationship with parental attitudes; mothers with high levels of ADHD symptoms of excessive reactive attitudes (over-reactive parenting) demonstrated by mothers of ADHD in children, ADHD symptoms and higher symptom levels in terms of late-term negative parental attitudes are found to be the decisive factors (29). A study conducted by Woods et al. (30) found that 79 children and their mothers with an age range of 5-10 were positively associated with maternal ADHD symptoms; high control level, low temperature (harsh parenting) parental attitudes, and there was no significant association between maternal ADHD levels and positive parental attitudes (30). A meta-analysis study that examined 32 studies on the subject found that negative parental attitudes and ADHD symptom levels were associated; their parents displayed high levels of control (hars parenting) and/or low levels of control and control (lax parenting) as ADHD levels increased.

In addition, it was determined that there was no significant relationship between parents' ADHD level and positive parental attitudes (31). In Turkey, 87 children with ADHD and a thesis study with 84 healthy control group; it has been found that mothers in the ADHD group exhibit more authoritarian and permissive attitudes than mothers in the control group, and ADHD symptom levels of mothers are associated with negative parental attitudes (26). In our study, parents with high levels of ADHD symptoms according to parents with a low level of ADHD symptoms, permissive attitudes to high levels of authoritarian attitudes and positive (competent) have been found to show significant differences in terms of parental attitudes. Our results, partially compatible with the literature, suggest that ADHD signs and symptoms negatively affect parental attitudes. ADHD is a disorder that causes attention deficit, difficulty in executive function, impulsivity, and difficulty in controlling emotions and behaviors (8). It is believed that possible difficulties in ADHD-induced control mechanisms and behavior regulation can prevent parents from developing stable attitudes in their relationship with their children, causing them to behave more permissively and unsupervised.

In studies conducted in children with ADHD, it was found that parental attitudes are associated with many variables. A study conducted by Silva and colleagues found that while the relationship between the attitudes of 68 parents with children with ADHD between the ages of 6 and 11 was not found, it was directly related to critical/rejecting and permitting/negligent parental attitudes and additional behavioral problems in children (32). One hundred three ADHD children and their mothers in Turkey with ADHD subtypes in a study examined the relationship between parental attitudes; it was determined that children in the careless and compound subtype perceive their parents as more permissive/negligent, while children with the hyperactive subtype perceive their parents as more authoritarian (22). A recent cross-sectional study conducted in Turkey, which examined 58 ADHD, 30 healthy children and their parents, found that children in the ADHD group perceive their maternal and paternal attitudes as less relevant, unsupervised and more strict discipline than the control group. In the same study, it was determined that variables such as children's gender, ADHD symptom level, comorbidity had significant effects on parental attitudes; When the mother's age was controlled, it was observed that the difference between the children with ADHD and healthy children in terms of perceived parental attitudes did not change (18). In our study, no significant association was found between parental attitudes and the age and educational levels of parents. Although our results are consistent with the literature, the lack of a healthy control group in our study is a significant limitation in terms of interpretation of our results.

When the literature was examined, it was seen that mostly only mothers were evaluated in studies examining parents' ADHD symptoms and parental attitudes (10,14,30,33,34). Our study is one of the few studies that evaluated the ADHD symptom levels of mothers and fathers separately (13,15,35-38). A study conducted with 109 of the mothers and fathers of children with an age range of 2-12 followed by the diagnosis of ADHD found no significant difference between the level of ADHD symptoms and parental attitudes of parents (39). Similarly, the results of our study found that parents did not differ significantly in terms of ADHD symptom level and parental attitudes. It is believed that large sample studies are needed to interpret our results.

Study Limitations

Our study has some limitations. The small sample size of our study and the lack of a healthy control group are limitations. ADHD is a clinical diagnosis, but in our study, parents were evaluated for ADHD only with diagnostic tools with high validity and reliability. It is an important limitation that parents have not been made diagnostic evaluations by a psychiatrist in terms of both ADHD and other possible psychopathologies. The fact that future studies on this issue have a design with a wide sample, in which parents are evaluated in terms of co-diagnoses with a high incidence of ADHD, as well as the severity of children's ADHD symptoms, will increase the interpretability of the results.

CONCLUSION

In the results of our study; parents of children diagnosed with ADHD have more permissive attitudes, parents with high ADHD symptom levels and parents with low ADHD symptoms do not differ in authoritarian and competent attitudes, and there is a significant difference between mothers and fathers in terms of ADHD level and parental attitudes. It was found that there was no difference between the parents' age and education levels and their attitudes. Parental attitudes play an important role in the severity of symptoms in ADHD, accompanying psychiatric diseases, and the prognosis of the disorder. ADHD in children negatively affects parents' parenting skills. The results of our study suggest that the symptoms of ADHD of parents in children with ADHD should also be considered as another factor that negatively affects their parenting skills. It is known that multiple approach models, including psychopharmacological treatments for the clinical treatment of ADHD, as well as evaluation of parents' attitude and behavior patterns and necessary psychosocial interventions, are the most effective treatment methods. During the treatment process, interventions for the parents' attitudes; it is thought that evaluation of mother and/or father in terms of ADHD and psychoeducation about adult ADHD is important.

Ethics Committee Approval: The study was approved by the Ankara University Faculty of Medicine Ethics Committee (approval number: 9.02.2012).

Informed Consent: The children and their parents in the study group were informed about the purpose and method of the study and their written consents were obtained.

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Retrospective Evaluation of Patients Undergoing Cardiopulmonary Resuscitation in the Emergency Department

Ertuğrul Altınbilek[1], Mustafa Çalık[2], Miray Tümer[3], Ahmet Burak Erdem[3], Derya Öztürk[1]

[1]Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[2]İstanbul Gaziosmanpaşa Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[3]Ankara City Hospital, Clinic of Emergency Medicine, Ankara, Turkey

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ABSTRACT

Objective: In this study, we aimed to investigate demographic data of patients who were arrested in an emergency department and outside the hospital, who died despite effective cardiopulmonary resuscitation (CPR), how they were admitted to the emergency department, blood parameters, additional diseases, and duration of CPR.

Methods: Two hundred two patients whose complete records can be accessed were included in the study. Demographic data of patients, emergency department arrival patterns, vital signs, additional diseases, blood gas pH, lactate, base minus values, CPR duration and adrenaline doses used in CPR were recorded.

Results: Two hundred twenty-one (59.90%) of the patients were male and 81 (40.09%) were female. Of the men, 69 (57.02%) were in the emergency department and 52 (42.97%) were outside the hospital. Fifty (61.72%) of the women were arrested in the emergency department and 31 (32.27%) were arrested outside the hospital. The average age of men was 70 and the average age of women was 80. In the group with non-hospital arrest, there was a significant difference between base minus, lactate and pH values in arterial blood gas compared to the group with in-hospital arrest.

Conclusion: Cardiopulmonary arrest is a very important health problem that is common in emergency departments and has a high rate of mortality. The society should be made aware of early diagnosis, timely and correct intervention, and rapid transfer of arrested cases outside the hospital. Advanced age, concomitant comorbid diseases, and prolonged CPR times are directly associated with mortality.

Keywords: Cardiopulmonary arrest, mortality, blood gas

INTRODUCTION

A sudden loss of consciousness with the termination of hemodynamics due to the cessation of electrical activity in the heart and the subsequent deterioration of cerebral perfusion is called cardiopulmonary arrest (1). 56-80% of arrest cases are of cardiac origin (2). Adult patients often have an underlying ischemic heart disease. A third of patients with acute myocardial infarction die within the first hour of reaching the hospital.

Generally, fibrillated rhythms are responsible for most of these deaths (ventricular fibrillation or pulseless ventricular tachycardia)

ORCID IDs of the authors: E.A. 0000-0003-4201-8850; M.Ç. 0000-0002-3184-2943; M.T. 0000-0002-3917-0213; A.B.E. 0000-0002-3618-6252; D.Ö. 0000-0001-7318-0725.

Corresponding Author: Ertuğrul Altınbilek,
E-mail: ertugrulaltinbilek@gmail.com

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(3). Pulseless electrical activity and asystolic rhythms are the most common in hospital arrests (4).

Causes of non-cardiac arrest can often be considered as non-traumatic bleeding, pulmonary thromboembolism, malignancy, intracranial pathologies, trauma, intoxication, and drowning in water (5).

In non-hospital arrest cases, the prognosis is poor and survival remains 3-7% despite effective cardiopulmonary resuscitation (CPR). 69% of these patients are male (6). In patients admitted to the emergency department, cardiopulmonary arrest is a condition with high mortality that can occur at any time. If there is hypotension, tachycardia, tachypnea, mental status changes, decreased urine output and accompanying laboratory abnormalities (hypoxia, acidosis, hyponatremia, hyperkalaemia, increased creatinine) in the patient who is followed up in the emergency room, the possibility of arrest is high. In hospital arrests, non-cardiac pathophysiological processes continue and eventually cardiac arrest develops (7). Mortality is quite high in both out-of-hospital and in-hospital arrests, even with timely and effective CPR (7).

In this study, we aimed to investigate the demographic data, forms of admission to the emergency room, blood parameters, comorbidities and CPR times of patients who were arrested in an education and research hospital emergency room or who were arrested outside the hospital and were brought to the emergency department and died despite effective CPR.

METHODS

For this retrospectively planned study, approval was obtained from the Ethics Board from a Şişli Hamidiye Etfal Training and Research Hospital (approval number: 2691, date: 25.02.2020). Patient consent was not obtained due to the fact that the study was retrospective, that there were patients with exitus, and that it was conducted through laboratory data. After the approval of the ethics committee, patients who were brought to a Training and Research Hospital, Clinic of Emergency Medicine with cardiac arrest or who developed cardiac arrest in the emergency department, who could not respond despite the current CPR protocol, and died between 01.06.2018 and 01.06.2019 were scanned retrospectively. In accordance with the current advanced life support protocols, the information of the cases undergoing CPR was obtained from the emergency service referral forms, ambulance case forms, emergency service and hospital records. A total of 202 patients whose information was fully accessible were included in the study. Patients were divided into two groups as those who were arrested inside the emergency room and outside the emergency room. Patients who were arrested outside the emergency department were also examined in two subgroups as those who applied to the emergency room with their own vehicles and those who came by ambulance. Demographic data of patients, emergency department arrival patterns, vital signs, additional diseases, blood gas pH, lactate, base minus values, CPR duration and adrenaline doses used in CPR were recorded.

Statistical Analysis

The SPSS for Windows, Version 22 (IBM, Armonk, NY, USA) was used for statistical analysis. Kolmogorov-Smirnov test was used for normality of variables. Mean ± standard deviation (SD) was used for parameters with a normal distribution, and median [interquartile range (IQR)] was used for parameters that did not match the normal distribution. Student's t-test was used for parameters with normal distribution. Those who did not have a normal distribution were evaluated by the Mann-Whitney U test. Pearson's correlation coefficients were calculated for normally distributed parameters. Spearman correlation coefficients were calculated for parameters that were not normally distributed. A p-value of <0.05 was considered statistically significant. In the descriptive statistics of the data, mean ± SD, median lowest, highest, frequency and ratio values were used.

RESULTS

Two hundred two patients who came to the emergency medicine clinic as an outpatient arrest or who died while being followed in the emergency department and died despite effective CPR were included in the study. One hundred twenty-one of these patients (59.90%) were male and 81 (40.09%) were female. Sixty-nine (57.02%) of the men were arrested in the emergency room and 52 (42.97%) outside the hospital. Fifty (61.72%) of the women were arrested in the emergency room and 31 (32.27%) outside the hospital (Table 1).

Table 1. Characteristics of routine blood parameters according to where patient groups are arrested

	Median (IQR)			
Features	**In-hospital (n=119)**	**Out-of-hospital (n=83)**	**All patients (n=202)**	**p**
Age, median (IQR), time, year	77.0 (64.0-85.0), 19-98	73.0 (56.0-84.0), 19-94	71 (63-84), 19-98	0.347
Gender, male/female	69/50	52/31	121/81	0.507
Lactate	4.4 (2.6-7.1)	10.9 (8.0-14.0)	7.0 (3.5-11.6)	<0.001*
pH	7.03 (6.92-7.18)	7.31 (7.2-7.4)	7.2 (7.05-7.379)	<0.001*
K, mmol/L	5.2 (4.2-6.3)	4.5 (3.8-5.4)	4.7 (4.0-5.89)	<0.001*
BD, mmol/L	-12.1 [-18.8-(-)8.8]	-6.8 [-12.4-(-2.5)]	-9.84 (-14.5-4.0)	<0.001*
CPR duration,min	35.0 (30.0-50.0)	40.0 (30.0-50.0)	40.0 (30.0-50.0)	0.215

CPR: cardiopulmonary resuscitation, IQR: interquartile range, K: potassium, BD: base deficit

In the group with non-hospital arrest, there was a significant difference between base minus, lactate and pH values in arterial blood gas compared to the group with in-hospital arrest (Table 1).

Forty-five (54.21%) of the cases arrested outside the hospital were admitted to the emergency department with their own vehicles, while 38 (45.78%) were brought to the emergency department with 112 ambulances (Table 2).

The average age of men was 70 and the average age of women was 80. Among the cases of arrest outside the hospital, the average age of those who came by ambulance was 73, and the average age of those who came by their own vehicle was 67. The average age of the emergency room arrest cases was 77 (Table 2).

Basic demographic characteristics and additional diseases of patients with in-hospital arrest and patients with out-of-hospital arrest are summarized in Table 2. No significant differences were found between the two groups between age, sex, and duration of CPR. P-values were p=0.347, p male=0.140, female: p=0.923, p=0.215, respectively.

The most common accompanying disease was ischemic heart disease (66.60%) in the group with in-hospital arrest, and systemic hypertension in the group with out-of-hospital arrest (48.20%).

In addition, the relationship between blood gas parameters and CPR durations is summarized in Table 3.

DISCUSSION

Sudden cardiac death, which occurs as a result of cardiopulmonary arrest, especially outside the hospital, is a significant public health problem and is one of the leading causes of death near almost the entire world. Despite rapid and effective cardioplumoner resuscitation, both in and out of hospital, there is a high rate of mortality. The mortality rate in non-hospital arrests is above 90%, while in hospital arrests this rate ranges from 13-85% (8). Therefore, the community needs to be educated and aware about recognizing cardiac arrest and providing basic life support. In this study, we aimed to define the general characteristics of cardiopulmonary arrest cases with mortal observation in the emergency department.

Wallace et al. (9) found that 54.50% of the patients were male in their study on 4,789 cases who underwent CPR. Khan et al. (10) reported that 60% of the cases were male. A higher rate of cardiac

Table 2. Basic demographic and additional diseases of patient groups

	Median (IQR)				
Features	In-hospital (n=119)	Out-of-hospital (n=83)		All patients (n=202)	p
		Ambulance	Own vehicle		
Age, median (IQR), time, year	77.0 (64.0-85.0), 19-98	73.0 (56.0-84.0), 19-94	-	71 (63-84), 19-98	0.347
Male	76 (62.5-84)	73 (28)	67 (25)	70 (30)	0.140
Famele	80 (66.5-85)	80 (16)	81 (15)	80 (16)	0.923
Gender, male/female	69/50	49/30	3/1	121/81	0.507
Co-morbidity	-	-	-	-	-
Hypertension, (n, %)	15 (51.7%)	13 (44.8%)	1 (3.4%)	29	-
Diabetes mellitus, (n, %)	7 (50%)	7 (50%)	0 (0%)	14	-
Ischemic heart disease, (n, %)	20 (66.6%)	10 (33.3%)	0	30	-
Chronic kidney disease, (n, %)	8 (80%)	2 (20%)	0	10	-
Cancer, (n, %)	17 (89.4%)	2 (10.5%)	0	19	-
Cerebrovascular accident, (n, %)	7 (77.7%)	1 (11.1%)	1	9	-
Chronic obstructive pulmonary disease, (n, %)	8 (80%)	2 (620%)	0	10	-
Other, (n, %)	5 (71.4%)	2 (28.5%)	0	7	-

IQR: interquartile range

Table 3. Relationship between life expectancy and parameters of groups

	In-hospital (n=119)		Out-of-hospital (n=83)	
Parameters	r	p	r	p
Lactate	-0.252	0.006*	0.110	0.322
pH	0.119	0.199	0.046	0.680
BD, mmol/L	0.104	0.259	-0.134	0.226
K, mmol/L	0.084	0.364	0.008	0.941

Values less than p<0.05 were considered significant, r-values were calculated using the Spearman correlation test.

BD: base deficit, K: potassium

J Acad Res Med 2020;10(3):264-68

arrest in men depends on the fact that ischemic heart disease is more common in this sex than in women (11).

In the study conducted by Petrie et al. (12), in which out-of-hospital arrest cases were examined, Ontario Prehospital Advanced Life Support, the average age of out-of-hospital cardiac arrest cases was 68, and in the National Registry of Cardiopulmonary Resuscitation study conducted by Peberdy et al. (13), the mean age of in-hospital arrest was 67.60.

In our study, 59.90% of the cases were male when demographic data was examined. The average age of those with in-hospital arrest was 77, and the average age of those with out-of-hospital arrest was 73. These findings were consistent with other studies.

Cardiac arrests are divided into in-hospital and out-of-hospital. Emergency departments are where both in-hospital arrests are common and out-of-hospital arrests are intervened as a result of transfer to the hospital (14). Mortality in cardiac arrests that develop outside the hospital is usually associated with prehospital factors (15). Studies have shown that they are more likely to live in witness arrests (14,16).

In our study, it was determined that non-hospital arrests were mostly brought by patient relatives (54.21%). This suggests to us that society is incapable of recognizing cardiac arrest and using the 112 emergency system for this purpose. We think that there is a need for more training in using 112 emergency health services for the right purpose and basic life support in the society.

In addition, it is important to have accessible automatic external defibrillators in crowded areas and to train people who can use these devices.

The main factor affecting mortality is having multiple comorbid diseases with increasing age (17). In most of these cases, the most common accompanying comorbid disease is structural heart disease, particularly coronary atherosclerosis and/or cardiomegaly (18). In accordance with the medical literature, ischemic heart disease (30%) was detected in the majority of patients in our study (18-20). Co-morbidities accompanying the cases taken in the study are given in detail in Table 2.

A long period of resuscitation in patients undergoing CPR shows an increased mortality rate (20). Mortality is higher if the resuscitation attempt lasts longer than 10 minutes. In our study, the average duration of resuscitation was 40 minutes (30-50).

Hypoxia, which develops in tissues with the development of cardiac arrest and prolonged resuscitation times, leads to the use of anaerobic metabolism and an increase in lactate levels in the blood. Acute myocardial ischemia results in an increase in intracellular potassium ions (21). Therefore, in order to evaluate whether CPR applied to the patient is effective or not, the arterial blood gas and the patient's blood pH, potassium and lactate level, base deficiency should be followed while resuscitation procedures continue. In this study, the relationship between CPR duration and blood gas results is given in detail in Figure 1.

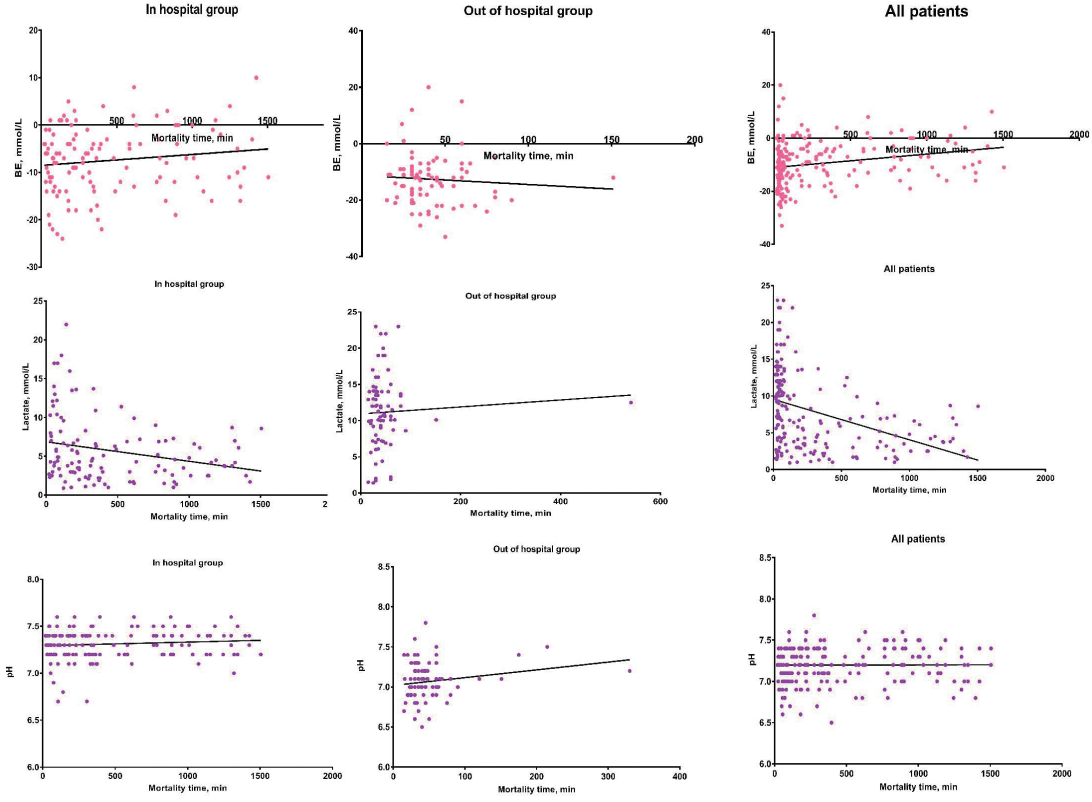

Figure 1. Relationship between CPR duration and blood gas results
CPR: cardiopulmonary resuscitation

Study Limitations

Because our study was retrospective and created study data for deceased patients, the control group could not be created. In addition, the fact that our sample numbers were small was also a factor that limited us.

CONCLUSION

Cardiopulmonary arrest is a very important health problem that is common in emergency departments and has a high rate of mortality. Community awareness should be raised about early recognition, timely and correct intervention, and rapid transfer to the hospital, especially cases that are arrested outside the hospital. Advanced age, concomitant co-morbid diseases, prolonged CPR durations are directly associated with mortality.

Ethics Committee Approval: For this retrospectively planned study, approval was obtained from the ethics board from a Şişli Hamidiye Etfal Training and Research Hospital (approval number: 2691, date: 25.02.2020).

Informed Consent: Patient consent was not obtained due to the fact that the study was retrospective, that there were patients with exitus, and that it was conducted through laboratory data.

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Follow-up for Patients with Intestinal Metaplasia Restricted to the Antrum

Deniz Öğütmen Koç[1], Sadettin Hülagü[2], Yeşim Saliha Gürbüz[3], Altay Çelebi[2], Ali Erkan Duman[2], Tanyeli Güneyligil Kazaz[4]

[1]University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Gastroenterology, İstanbul, Turkey
[2]Kocaeli University Faculty of Medicine, Department of Gastroenterology, İzmit, Turkey
[3]İstinye University Faculty of Medicine, Department of Pathology, İstanbul, Turkey
[4]Gaziantep University Faculty of Medicine, Department of Biostatistics, Gaziantep, Turkey

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ABSTRACT

Objective: Guidelines recommend endoscopic surveillance for patients with extensive atrophy/intestinal metaplasia (IM), but follow-up is not recommended for patients with atrophy/IM restricted to the antrum. We evaluated the risk of neoplastic lesions in patients with antrum-restricted IM to determine whether surveillance endoscopy is necessary.

Methods: Overall, 117 patients with antrum-restricted IM diagnosed within the past 10 years underwent surveillance endoscopy. The gastric biopsy specimens were evaluated for atrophy, IM, and dysplasia.

Results: We enrolled 117 patients. Surveillance endoscopy was performed at a median (interquartile range) of 7.2 years (5.9-8.7 years) after the initial diagnosis of IM. On surveillance endoscopy, 27.4% of patients exhibited progression in their IM grade, whereas 25.6% had atrophy progression, and 33.3% had dysplasia progression. High-grade dysplasia and gastric cancer (GC) were detected in four and two patients, respectively. The annual incidence of GC in patients with antrum-restricted IM was 0.17%. IM grade and type regressed in 29.9% and 38.5% of patients, respectively. Most patients with progressive IM grade, IM type, and dysplasia on surveillance endoscopy had Operative Link on Gastritis Assessment (OLGA) stage 3-4 (p=0.0001, p=0.008, and p=0.0001, respectively), and most patients with progressive atrophy and dysplasia had Operative Link on Gastric IM (OLGIM) stage 3-4 (both p=0.001).

Conclusion: Patients with IM restricted to the antrum are at risk for neoplastic lesions and require endoscopic surveillance, contrary to existing recommendations. Premalignant lesions can exhibit both progression and regression. Therefore, a patient-specific surveillance program based on OLGA and OLGIM might be appropriate.

Keywords: Gastric cancer, intestinal metaplasia, surveillance endoscopy

INTRODUCTION

Gastric cancer (GC) is one of the most common cancers globally and has a poor prognosis, especially in the advanced stages of the disease. Nevertheless, screening and monitoring patients at risk of GC can facilitate early detection and treatment and reduce mortality (1).

Intestinal-type gastric adenocarcinoma is the final stage of a multi-stage disease process known as the Correa cascade, which includes

ORCID IDs of the authors: D.Ö.K. 0000-0003-2738-625X; S.H. 0000-0001-6659-1286; Y.S.G. 0000-0002-4278-8241; A.Ç. 0000-0003-2864-7124; A.E.D. 0000-0002-7093-2503; T.G.K. 0000-0002-4191-1244.

Corresponding Author: Deniz Öğütmen Koç,
E-mail: drdenizkoc@gmail.com

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inflammation, atrophy, intestinal metaplasia (IM), dysplasia, and carcinoma (2). IM is a precancerous lesion characterized by replacement of the epithelium in the oxyntic or antral mucosa with intestinal epithelium. IM is classified as complete (small-intestine type) or incomplete (colonic type; thought to be the most advanced stage of IM) based on the histologic characteristics and type of mucinous material secreted (3). Notably, patients with gastric IM, along with other precancerous gastric lesions, are better monitored in Asia than in Europe (4). New guidelines for screening programs were published recently in Western countries (5,6). However, a study conducted in the United States revealed that 78% of endoscopists were not aware of the guidelines for the surveillance and management of IM (7). Notably, the best strategy for reducing mortality in patients at high risk of GC is diagnosis and surveillance of precancerous gastric lesions (8,9). The recently presented guidelines recommend endoscopic surveillance for patients with extensive atrophy and/or IM (5,6,10). However, no scheduled endoscopic and histologic surveillance was recommended for patients with antrum-restricted IM and atrophy (6,11). However, to the best of our knowledge, no comprehensive study has been conducted regarding the follow-up of patients with premalignant gastric lesions restricted to the antrum.

Our study evaluated the risk of neoplastic lesions in patients with antrum-restricted IM to determine whether surveillance endoscopy is necessary.

METHODS

For this single-center study, we invited patients with antrum-restricted IM that had been histologically confirmed with untargeted biopsy sampling in the past 10 years to undergo targeted biopsy sampling during surveillance endoscopy. We selected patients with at least 4 years between the initial and surveillance endoscopies. Overall, 607 patients were identified. We excluded patients with peptic ulcers, Barrett's esophagus, GC, other cancers, and prior gastric resection. In addition, we excluded patients whose initial gastric biopsy did not meet the minimum quality criteria (e.g., paraffin block for a reassessment of the antrum mucosa) and those who could not be reached by telephone. We called up 182 patients and invited them to undergo surveillance endoscopy; of these, 117 agreed and were included in the study. During the appointment, patients were asked about their smoking history, use of non-steroidal anti-inflammatory drugs (NSAIDs), use of proton pump inhibitors (PPIs), diagnosis and treatment of *Helicobacter pylori (H. pylori)* infection, and family history of GC. For consistency, all esophagogastroduodenoscopy and biopsy procedures were performed by a single physician (D.O.K.).

For optimal assessment of the severity and distribution of premalignant gastric lesions, biopsies were obtained from five standardized intragastric locations during surveillance endoscopy according to a predetermined protocol (12) (Figure 1). Overall, the following 12 biopsies were obtained: 4 from the pylorus 2-3 cm proximal to the antrum, 2 from the opposite walls of the incisura angularis, 2 from the corpus minor curvature, 2 from the corpus greater curvature, and 2 from the cardia. Additional targeted biopsies were obtained of visible abnormalities and lesions in the stomach, if present.

IM was graded according to the visual analog scale of the updated Sydney system (0: absent; 1: mild; 2: moderate; 3: marked). Mucosal atrophy score was evaluated on a four-level scale [no atrophy (0%) score=0; mild atrophy (1-30%) score=1; moderate atrophy (31-60%) score=2; and severe atrophy (>60%) score=3] (3). In addition, the Vienna system was used to classify dysplasia as low- or high-grade neoplasia (13). For histopathologic examination, preparations were stained with hematoxylin-eosin and Alcian blue–periodic acid Schiff (pH 2.5). Giemsa staining was performed to identify *H. pylori* infection. The biopsy samples obtained during the first endoscopy were re-evaluated by the same pathologist (Y.S.G.), independent of any subsequent biopsy. Because different lesion grades often coexist in pathologic specimens obtained from the same patient, the highest grade lesion observed in any biopsy specimen was used to grade the disease in each patient. IM was subclassified, based on the morphologic characteristics, as "complete" (presence of mature brush border absorptive cells, sialomucin-secreting goblet cells and, occasionally, Paneth cells) or "incomplete" (few absorptive cells, secretion of sulfomucin by intermediate cells, secretion of sialomucin and/or sulfomucin by goblet cells, and marked glandular distortion and branching in the metaplastic glands) (14).

The Operative Link on Gastritis Assessment (OLGA) staging system was used to determine the disease status according to the antrum and corpus scores. The disease was graded on a scale ranging from stage 0 (none) to stage 4 (severe) (15). For the Operative Link on Gastric Intestinal Metaplasia (OLGIM) system, IM was evaluated instead of atrophy, and the severity and distribution of IM were classified on a scale ranging from stage 0 (none) to stage 4 (severe) (16). Patients with stage 3-4 disease on OLGA and OLGIM were considered at high risk of GC.

This study was approved by the Kocaeli University Faculty of Medicine Local Ethics Committee (approval number: 4, date: 2011). Informed consent was obtained.

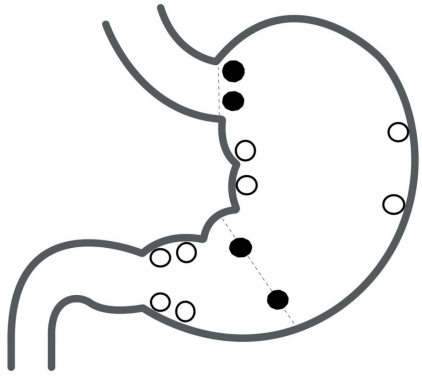

Figure 1: Biopsy sites (adapted from reference 12)

J Acad Res Med 2020;10(3):269-76

Statistical Analysis

Statistical analysis was performed using SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA). We used the Shapiro-Wilk test to determine if numerical variables followed a normal distribution. The Wilcoxon test was used to evaluate the dependent numerical variables that were not normally distributed. The relationship between categorical variables was determined using the chi-square analysis. Relationships between numerical variables were tested using the Spearman's rank correlation coefficient. Numerical variables are expressed as mean and standard deviation, and categorical variables are expressed as numbers and percentages. A p-value <0.05 indicated statistical significance.

RESULTS

Baseline Characteristics at Initial Endoscopy

The study included 117 patients with IM restricted to the antrum, with or without atrophy on initial endoscopy, which was performed at the Department of Gastroenterology, Kocaeli University Faculty of Medicine. The median [interquartile range (IQR)] age of patients at the time of surveillance endoscopy was 59 years (49-67 years), and 57.3% of patients were women. At baseline, 95 patients (81%) had a histologic diagnosis of atrophy, 79 (67.5%) had incomplete IM, 38 (32.5%) had complete IM, and 19 (16.2%) had low-grade dysplasia (LGD). On initial endoscopy, 41.0% of patients had *H. pylori* infection, of which 44.8% had undergone *H pylori* eradication therapy after initial endoscopy. Overall, 51.7% of patients were smokers, 36.8% were using NSAIDs, and 69.2% were on PPIs at initial endoscopy. One-quarter (25.0%) of patients had a family history of GC. Nevertheless, no relationship was noted between history of GC and IM type (p=0.301) or IM grade (p=0.929) (Table 1).

Surveillance Endoscopy

Surveillance endoscopy was performed at a median (IQR) of 7.2 years (5.9-8.7) after the initial diagnosis of IM. On initial endoscopy, 22 patients had antrum-restricted IM with atrophy, and 95 patients had no atrophy. On surveillance endoscopy, the rates of dysplasia were similar between patients with and without atrophy (p=0.339). IM was absent in 22 patients (18.8%) on surveillance endoscopy. Among the 95 patients with IM, 58.9% of patients had IM present in only the antrum or incisura angularis, 4.2% in the corpus, and 36.8% had in both regions.

Surveillance endoscopy revealed high-grade dysplasia (HGD) in four patients (3.4%) with previous indefinite dysplasia and gastric adenocarcinoma in two patients (1.7%) with previous LGD. The annual incidence of GC in patients with antrum-restricted IM was 0.17%. In the first patient with gastric adenocarcinoma, diffuse gastric carcinoma was detected in the incisura angularis 4.6 years after the initial endoscopy, and surgery was performed. In the second patient, an intestinal-type early gastric carcinoma was detected 4.7 years after onset, and endoscopic submucosal dissection was performed.

Progression and Regression of Premalignant Lesions

On surveillance endoscopy, 11.1% of patients exhibited progression of IM type, 27.4% had progression of IM grade, 25.6% had progression of atrophy, and 33.3% had progression of dysplasia compared with the results of the initial endoscopy. Compared with the findings on initial endoscopy, IM type regressed in 38.5% of patients, and IM grade regressed in 29.9%. Notably,

Table 1. Baseline characteristics of the 117 patients

Age, mean (± SD), y	58.26±11.2
Sex	
Male	50 (42.7)*
Female	67 (57.3)*
IM type	
Complete	38 (32.5)*
Incomplete	79 (67.5)*
IM grade	
Mild	48.0 (41.0)*
Moderate	48.0 (41.0)*
Marked	21 (18.0)*
Atrophy	
None	22 (18.8)*
Mild	65 (55.5)*
Moderate	26 (22.2)*
Marked	4 (3.4)*
Dysplasia	
None	31 (26.5)*
Undefined	67 (57.3)*
Low grade	19 (16.2)*
Helicobacter pylori	
Negative	69 (59)*
Positive	48 (41)*
Family history of gastric cancer	
Yes	29 (25.0)*
No	87 (75.0)*
NSAIDs	
Yes	43 (36.8)*
No	74 (63.3)*
Proton pump inhibitors	
Yes	81 (69.2)*
No	36 (30.8)*
Smoking	
Yes	60 (51.7)*
No	56 (48.3)*
Alcohol consumption	
Yes	13 (11.2)*
No	103 (88.8)*

*(n, %), IM: intestinal metaplasia, NSAIDs: non-steroidal anti-inflammatory drugs, SD: standard deviation

IM type and grade were stable in 50.4% and 42.7% of patients, respectively. Similarly, atrophy regressed in 35.0% of patients, and atrophy was stable in 39.3% based on surveillance endoscopy; dysplasia regressed in 23.1% of patients, and dysplasia was stable in 43.6% (Table 2). Among patients with incomplete metaplasia on initial endoscopy, 54.0% had incomplete IM on surveillance endoscopy, 25.3% had complete IM, and 20.3% did not have IM. Among the patients with complete IM on initial endoscopy, 34.2% progressed to incomplete metaplasia, and 23.7% did not have IM.

On surveillance endoscopies, a positive correlation was observed between the progression of the IM grade and the progression of the IM type (r=0.59, p=0.001), atrophy (r=0.52, p=0.001), and dysplasia (r=0.55, p=0.001). Likewise, as IM type progression, both atrophy (r=0.22, p<0.05) and dysplasia progressed (r=0.41, p=0.001). Moreover, as atrophy progressed, dysplasia progressed too (r=0.53, p=0.001).

Progression to Dysplasia in Premalignant Lesions

A statistically significant difference was observed between IM grade on the initial biopsies and the distribution of dysplasia in subsequent biopsies (p=0.002) and between atrophy status on the initial biopsies and the distribution of dysplasia in subsequent biopsies (p=0.019). Fourteen patients (43.8%) who had LGD on surveillance endoscopy, as well as all four patients with HGD (100%) and two patients with GC (100%), had moderate IM on initial endoscopy. However, 23 patients (56.1%) without dysplasia and 17 (44.7%) with indefinite dysplasia had mild IM on initial endoscopy (p=0.002). Likewise, 13 patients (40.6%) with LGD and 2 patients (100%) with GC had moderate atrophy scores on the initial biopsies. Moreover, 20 patients (48.8%) without dysplasia and 28 patients (73.7%) with indefinite dysplasia had mild atrophy scores on the initial biopsies (p=0.019). No significant relationship was noted between IM type on the initial biopsies and the distribution of dysplasia on subsequent biopsies (p=0.070) (Table 3). However, 24 of 32 patients (75%) who had LGD on surveillance endoscopy had incomplete IM on initial endoscopy, and in all 4 patients (100%) with HGD and both patients (100%) with GC on surveillance endoscopy, incomplete IM was noted on initial endoscopy.

Risk Factors

The rate of *H. pylori* infection was significantly higher on surveillance endoscopy compared with initial endoscopy (p=0.001). Notably, including the 23 patients who received eradication therapy before initial endoscopy, 53 patients (76.8%)

Table 2. Progression and regression of premalignant gastric lesions on surveillance endoscopy

	Surveillance endoscopy n (%)		
	Progression	**Regression**	**No change**
Baseline endoscopy			
IM types	13 (11.1)	45 (38.5)	59 (50.4)
IM grade	32 (27.4)	35 (29.9)	50 (42.7)
Atrophy	30 (25.6)	41 (35)	46 (39.3)
Dysplasia	39 (33.3)	27 (23.1)	51 (43.6)

IM: intestinal metaplasia

Table 3. Comparison of patients at low and high risk for gastric cancer on surveillance endoscopy according to histologic characteristics on initial endoscopy

Dysplasia on surveillance endoscopy, n (%)						
Baseline endoscopy	**GC (n=2)**	**HGD (n=4)**	**LGD (n=32)**	**Indefinite (n=38)**	**None (n=41)**	**p**
IM grade						
Marked	0	0	10 (31.3)	7 (18.4)	4 (9.8)	-
Moderate	2 (100)	4 (100)	14 (43.8)	14 (36.8)	14 (34.1)	0.002*
Mild	0	0	8 (25)	17 (44.7)	23 (56.1)	-
IM type						
Incomplete	2 (100)	4 (100)	24 (75)	25 (65.8)	24 (58.5)	0.070
Complete	0	0	8 (25)	13 (34.2)	17 (41.5)	-
Atrophy						
Marked	0	0	1 (3.1)	0	3 (7.3)	-
Moderate	2 (100)	0	13 (40.6)	4 (10.5)	7 (17.1)	-
Mild	0	4 (100)	13 (40.6)	28 (73.7)	20 (48.8)	0.019*
None	0	0	5 (15.6)	6 (15.8)	11 (26.8)	-

*p<0.05 indicates significance.
GC: gastric cancer, HGD: high-grade dysplasia, IM: intestinal metaplasia, LGD: low-grade dysplasia

J Acad Res Med 2020;10(3):269-76

without *H. pylori* infection had positive *H. pylori* results on surveillance endoscopy.

Nevertheless, no correlation was noted between the progression and regression status of premalignant lesions and possible risk factors, such as age, sex, smoking history, alcohol use, PPI and NSAID use, and *H. pylori* infection (all p>0.05).

OLGA and OLGIM Stage

On surveillance endoscopy, 32.8% of patients had OLGA stage 1 disease, 24.1% had stage 2, 10.3% had stage 3, and 1.7% had stage 4. No significant relationship was observed between IM grade (p=0.064), IM type (p=0.593), atrophy (p=0.222), or dysplasia distribution (p=0.138) on initial endoscopy and the OLGA stages on surveillance endoscopy. However, on surveillance endoscopy, OLGA stage 3-4 disease was noted in most patients who had progression of IM grade (p=0.0001), IM type (p=0.008), and dysplasia (p=0.0001).

On surveillance endoscopy, 19 patients (16.2%) had OLGIM stage 1, 41 (35%) had stage 2, 22 (18.8%) had stage 3, and 14 (12%) had stage 4. Furthermore, with the increase in IM grade, IM type, atrophy, and dysplasia on initial endoscopy, an increase in OLGIM stage was observed on surveillance endoscopy. Most patients with OLGIM stage 2-4 disease had incomplete IM, and LGD, or indefinite dysplasia on initial endoscopy, whereas most OLGIM stage 1 patients had complete IM (p=0.044) and no dysplasia (p=0.009) (Table 4).

Regarding the OLGIM stage of premalignant lesions on surveillance endoscopy, moderate atrophy was noted in most patients with OLGIM stages 3 (59.1%) and 4 (50.0%); stage 2 was seen in most patients (56.1%) with mild atrophy, and atrophy was not observed in most patients with stage 1 (63.2%) (p=0.001). Incomplete IM was observed in most patients with OLGIM stages 2 (51.2%), 3 (86.4%), and 4 (85.7%), and complete IM was observed in most patients with stage 1 (73.7%) (p=0.001). Regarding dysplasia, LGD was noted in most patients with stages 3 (50.0%) and 4 (57.1%), and nearly half (48.8%) of patients with indeterminate dysplasia had stage 2. Typically, dysplasia was not observed in patients with stage 1 (p=0.001).

Furthermore, most patients whose atrophy progressed on surveillance endoscopy had OLGIM stages 3 (45.5%) and 4 (42.9%) (p=0.001), and those whose dysplasia progressed were OLGIM stages 3 (50.0%) and 4 (64.3%) (p=0.001).

DISCUSSION

In this study, patients with antrum-restricted IM on untargeted biopsies obtained during initial endoscopy were re-evaluated after a median of 7.2 years. Based on our results, patients with antrum-restricted IM are at risk of neoplastic lesions and require endoscopic surveillance. In addition, it has been observed that premalignant lesions can both progress and regress during clinical surveillance.

Table 4. Evaluation of OLGIM stages on surveillance endoscopy according to histology diagnoses on baseline endoscopy

OLGIM on surveillance endoscopy, n (%)						
Baseline endoscopy	**Stage 4**	**Stage 3**	**Stage 2**	**Stage 1**	**None**	**p**
IM grade						
Marked	6 (42.9)	7 (31.8)	5 (12.2)	1 (5.3)	2 (9.5)	-
Moderate	6 (42.9)	9 (40.9)	22 (53.7)	3 (15.8)	8 (38.1)	0.001*
Mild	2 (14.3)	6 (27.3)	14 (34.1)	15 (78.9)	11 (52.4)	-
IM type						
Incomplete	12 (85.7)	19 (86.4)	26 (63.4)	9 (47.4)	13 (61.9)	0.044
Complete	2 (14.3)	3 (13.6)	15 (36.6)	10 (52.6)	8 (38.1)	-
Atrophy						
Marked	0 (0.0)	1 (4.5)	0 (0.0)	1 (5.3)	2 (9.5)	-
Moderate	5 (35.7)	5 (22.7)	11 (26.8)	0 (0.0)	5 (23.8)	0.043
Mild	8 (57.1)	11 (50.0)	25 (61.0)	13 (68.4)	8 (38.1)	-
None	1 (7.1)	5 (22.7)	5 (12.2)	5 (26.3)	6 (28.6)	-
Dysplasia						
High-grade	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Low grade	4 (28.6)	6 (27.3)	5 (12.2)	1 (5.3)	3 (14.3)	0.009*
Indefinite	9 (64.3)	11 (50.0)	29 (70.7)	6 (31.6)	12 (57.1)	-
None	1 (7.1)	5 (22.7)	7 (17.1)	12 (63.2)	6 (28.6)	-

*p<0.05 indicates significance.
IM: intestinal metaplasia , OLGIM: Operative Link on Gastric Intestinal Metaplasia

Delayed diagnosis of GC is associated with a high mortality rate. Therefore, it is imperative to screen for premalignant lesions in high-risk groups (17). Moreover, an uneven IM distribution might cause sampling errors, making the detection of premalignant gastric lesions challenging. Therefore, the best approach is to use diagnostic endoscopy with a gastric mapping protocol. The updated Sydney system is a widely applied biopsy protocol (7). However, studies have reported that this protocol does not fully reflect the actual state of IM (18,19). Therefore, in our study, we used a biopsy protocol to obtain specimens from all stomach regions to optimally assess the severity and distribution of premalignant gastric lesions (12). Most premalignant gastric lesions were observed in the antrum, followed by throughout the stomach and the corpus. In Western countries and other populations, 50% of precancerous gastric lesions were noted in the antrum, 17.7% in the corpus, and 15% in both regions (20,21).

Notably, the prevalence of GC varies significantly among different geographic regions (22,23). Guidelines recommend surveillance endoscopy for patients with extensive IM and atrophy, and also for patients with gastric IM who are at high risk for GC owing to their ethnicity or family history (5,6,10,11). European guidelines recommend an interval of 3 years and more more intensive surveillance for those with extensive gastric IM and atrophy, whereas the guidelines of the American Gastroenterological Association recommend a 3- to 5-year surveillance period (5,6). Nonetheless, these guidelines do not recommend follow-up for patients with antrum-restricted gastric IM and atrophy. However, in our study, 27.4% of patients with antrum-restricted IM on initial endoscopy had progression of the IM grade, whereas 25.6% had progression of atrophy and 33.3% had progression of dysplasia on surveillance endoscopy. In addition, HGD and GC were detected in four and two patients, respectively. For the two patients with GC, the mean time between initial endoscopy and GC diagnosis was 4.65 years. In our series, the annual incidence of GC was 0.17% among patients with antrum-restricted IM. In one study, the 10-year incidence of GC was 0.8% among patients with atrophic gastritis, while that of patients with IM was 1.8% (8). Therefore, it might not be appropriate to use the same follow-up period for patients with atrophic gastritis and IM. However, per another study, no patients with atrophic gastritis or complete IM on their initial biopsies developed HGD or GC during the 3-year follow-up period, with only less than 10% of cases progressing to LGD (24). Nevertheless, the annual endoscopic follow-up might not be appropriate for all patients with IM because some will not develop GC. Therefore, a better approach would be to devise a patient-individualized follow-up strategy.

Although the US guidelines on surveillance endoscopy consider patients with incomplete IM as high risk, the European guidelines and the study of Dinis-Ribeiro et al. (11) do not consider IM type (5,6,12). Gonzalez et al. (25) revealed that the risk of GC is three times higher in patients with incomplete IM than those with complete IM. In another study from Spain, 16 of 21 patients with adenocarcinoma had incomplete IM at a mean of 12.8 years after the initial diagnosis, and 1 patient had complete IM; the risk of GC was highest among patients with incomplete IM, and a family history of GC (26). In our study, all four patients with HGD and two with GC, diagnosed on surveillance endoscopy, had incomplete metaplasia on the initial endoscopy. Dinis-Ribeiro et al. (11) suggested using IM grade instead of IM subtype. However, we determined a positive correlation between IM type and grade in our study. Notably, with the progression of IM type, the IM grade and dysplasia also progressed. Therefore, contrary to recommendations, patients with complete IM in the antral mucosa, a history of smoking, a family history of GC, or incomplete IM restricted to the antrum would require endoscopic surveillance (27).

While some precancerous gastric lesions show progression, others may remain stable, or exhibit true regression or show false regression according to the characteristics of the biopsy sampling site or interpretation of histologic grades (21,28). Our data indicated that premalignant lesions might exhibit both progression and regression on clinical surveillance. In our series, based on the findings of the initial endoscopies, 38.5% of patients had IM type regression, and 29.9% had IM grade regression. Nevertheless, IM type remained stable in 50.4% of patients, and IM grade remained stable in 42.7. Similarly, 35% of patients had atrophy regression, and 39.3% had persistent atrophy, whereas 23.1% of patients had dysplasia regression, and 43.6% had persistent dysplasia. Studies have revealed that the location, severity, and extent of precancerous lesions, particularly IM, reflect the likelihood of progression to GC (29). Contrary to some studies stating that IM does not regress, recent studies have demonstrated that IM can be reversible (30,31). When Akbari et al. (28) used a random-effects model to review 20 studies on patients with IM, they reported that the IM regressed in 31.8%, whereas it remained stable in 43.4%. When the results of 10 studies were combined, 32.2% of patients had atrophy regression, and 38.8% had persistent atrophy (28). In addition, the characteristics of LGD and regenerative changes exhibit a large overlap, which could complicate the diagnosis of LGD (32,33). Nevertheless, a study that followed up patients with dysplasia for more than 2 years noted that among patients with LGD, 21% had progression and 36% had spontaneous regression, and in those with moderate-grade dysplasia, 33% had progression, and 27% had spontaneous regression. In addition, 43% of cases with severe dysplasia remained stable, 47% progressed to GC, and 0% regressed (34). Strikingly, den Hoed et al. (19) revealed that 67% of cases of LGD regressed to IM, and the remaining third had regression to atrophic gastritis and even normal mucosa on surveillance endoscopy.

In our study, the severity and extent of premalignant lesions detected on initial endoscopy were not associated with OLGA stage but were associated with OLGIM stage. On initial endoscopy, we observed that, as the severity of IM grade, IM type, atrophy, and dysplasia increased, so did the OLGIM stage on surveillance endoscopy. In addition, patients whose premalignant lesions exhibited progression on surveillance endoscopy had

J Acad Res Med 2020;10(3):269-76

OLGA and OLGIM stages 3-4. Some experts recommend using a combination of OLGA and OLGIM to stage chronic gastritis (35). In addition, for patients with extensive atrophy/IM in both the antrum and corpus, histopathologic staging systems, such as OLGA and OLGIM, could be useful for defining patient subgroups based on the risk of progression to GC (11). Our results suggest that the OLGA and OLGIM staging systems can be used in the follow-up programs for premalignant gastric lesions.

Study Limitations

Nonetheless, our study had some limitations. Although premalignant lesions might develop into neoplastic lesions over the long term, we cannot be definitive regarding the likelihood of this transition, owing to our limited number of patients. In addition, because precancerous lesions have multifocal involvement, we cannot exclude sampling error and misclassification. Another limitation of our study was that we used regular white-light endoscopy at both baseline and surveillance. Although recent guidelines recommend the use of narrow-band imaging to detect premalignant gastric lesions (11), we use white-light endoscopy in our daily practice. Nevertheless, the strength of this study was that the biopsy specimens were obtained by a single physician to ensure consistency. Moreover, analysis of these biopsy samples by a single experienced pathologist ruled out interobserver variability.

CONCLUSION

Patients with antrum-restricted IM are at risk of neoplastic lesions and require endoscopic surveillance, contrary to the existing recommendations. Moreover, instead of using a single surveillance program to evaluate all patients, a more appropriate approach would be to use a patient-specific follow-up program and use OLGA and OLGIM criteria to determine follow-up intervals. Our data revealed that premalignant lesions might exhibit both progression and regression during clinical surveillance. In addition, our study indicated that the IM subtype, along with IM grade, is a useful marker in identifying patients at risk for GC.

Ethics Committee Approval: This study was approved by the Kocaeli University Faculty of Medicine Local Ethics Committee (approval number: 4, date: 2011).

Informed Consent: It was obtained.

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Reliability and Validity of the Turkish Version of the Questionnaire for the Assessment of Self-Reported Olfactory Functioning and Olfaction-Related Quality of Life

Özlem Saatçi[1], Özge Arıcı Düz[2], Aytuğ Altundağ[3]

[1]University of Health Sciences Turkey, Sancaktepe Şehit Prof Dr. İlhan Varank Training and Research Hospital, Clinic of Otolaryngology, İstanbul, Turkey
[2]Medipol University Faculty of Medicine, Department of Neurology, İstanbul, Turkey
[3]Biruni University Faculty of Medicine, Department of Otolaryngology, İstanbul, Turkey

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ABSTRACT

Objective: To examine the reliability and validity of the Turkish version of the questionnaire for the assessment of self-reported olfactory functioning and olfaction-related quality of life (ASOF).

Methods: Three different surveys [ASOF, beck depression inventory (BDI), and 36-Item Short-Form Health Survey (SF-36) questionnaire] were completed by 112 subjects with subjective olfactory dysfunction (OD) and 21 healthy controls. Sniffin' Sticks tests were performed. Internal consistency, test-retest reliability, and validity were analyzed.

Results: The Cronbach α coefficients for the ASOF self-reported capability of perceiving (ASOF-SRP) specific odors scale (SOC) and ASOF self-reported olfaction-related quality of life (ASOF-ORQ) were 0.98 and 0.97, with relatively high internal consistency, respectively. The test-retest reliability for the ASOF was high for all subscales. ASOF-SRP-SOC, ASOF-SRP, and ASOF-ORQ showed significant positive correlations with the overall SF-36 score and negative correlations with BDI. The ASOF scale scores in healthy controls were significantly higher than those in patients with hyposmia and anosmia (p=0.001). TDI composite score and its subscales (threshold, discrimination, and identification) showed significant negative correlations with the BDI score and significant positive correlations with each of the SF-36 domains and overall SF-36 scores and ASOF subtests.

Conclusion: This study showed that the Turkish version of the ASOF is a reliable and valid measure to determine the olfactory function and impairment in daily life associated with OD. Because of the easy-to-use features of the ASOF, it is a useful tool for initial assessment and follow-up of the subjects with OD.

Keywords: Smell, olfaction disorders, quality of life, olfactory test, olfaction-related quality of life, questionnaire of olfactory disorders

INTRODUCTION

The prevalence of olfactory dysfunction (OD) in the general population ranges between 4% and 25% (1). Sinonasal disorders, upper airway infections, and trauma are the most frequent causes of OD (2). OD not only leads to a decline in tasting foods, but also may affect an individuals' life by complicating the recognition of rotten food or toxic gases (3). Moreover, OD may influence subjects' well-being and health-related quality of life and may even lead to the development of depression in some individuals (4).

ORCID IDs of the authors: Ö.S. 0000-0002-3372-9514; Ö.A.D. 0000-0003-0334-811X; A.A.0000-0003-0794-5050.

Corresponding Author: Özlem Saatçi,
E-mail: oreleos@hotmail.com

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Psychometric assessment tools have been developed to evaluate the individual effects of OD on daily activities. Questionnaire for olfactory dysfunction (QOD), olfaction questionnaire, and assessment of self-reported olfactory functioning and olfaction-related quality of life (ASOF) are some of the tests used to evaluate the functional status and health-related quality of life following OD (3-7). ASOF was developed by Pusswald et al. (4) in 2012. ASOF contains subjective olfactory capability scale (SOC), self-reported capability of perceiving specific odors scale (SRP), and olfactory-related quality of life scale (ORQ). Besides its feasibility for application to subjects with OD, ASOF can also provide data concerning the psychometric properties of subjects with OD. ASOF, which is used to assess patients' subjective symptom severity in clinical practice, has been shown to discriminate between subjects with normosmia and hyposmia (8,9).

Disease-specific questionnaires evaluating the quality of life may be utilized to identify the changes in the health-related quality of life. Moreover, these inventories may help compare data derived from different populations. However, the content and language of the questionnaires have to be adapted and tested before its application in different patient populations. Therefore, the present study aimed to assess the validity and reliability of the Turkish version of the ASOF in subjects with OD.

METHODS

This prospective single-center study was conducted on 112 subjects admitted to the Smell and Taste Center for subjective smell disorders between March 2019 and December 2019. The control group included 21 healthy subjects without any chronic medical disease or OD. All subjects underwent routine otolaryngological examination, nasal endoscopy, computed tomography of the paranasal sinuses, and Sniffin' Sticks test. Subjects with neurodegenerative diseases, pregnant subjects, smokers, and subjects with malignancies were excluded. Ethics committee approval was received for this study from the Ethics Committee of Medipol University (approval number: 268, date: 22.03.2019). The study was conducted in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

In the test-retest reliability analysis, the data related to 50 individuals were analyzed through the Spearman correlation test and compared with the data obtained after 3 weeks.

Olfactory Function Tests

The Turkish version of the Sniffin' Sticks test (Burghart, Wedel, Germany) was used to evaluate patients' olfactory function. The cap of the pen was removed by the experimenter to present odor for 3 s while the tip of the pen was 1-2 cm away from the nostrils. Odor thresholds (T) for n-butanol were determined by using three alternative forced-choice procedures. Sixteen triplets of pens were presented for odor discrimination (D), one containing 4% n-butanol solution (target odorant), and the other two containing only propylene glycol (negative controls). The subjects were requested to identify the pen containing the odorant. Each odor was presented once. The subjects were blindfolded using a sleeping mask to prevent visual identification of the pens. At least 30-s intervals were provided between odor samplings. The answer was accepted as correct when the subject could identify the pen containing the odorant for two consecutive applications. T was scored from 1 to 16.

Sixteen common odors were used to assess odor identification (OI). OI was performed from a list of four verbal descriptors using a multiple forced-choice paradigm. Each odorant was presented by the experimenter with 30-s intervals between odors. OI was scored from 0 to 16.

Overall olfactory function (TDI score) was expressed by adding the scores from the three individual tests, and scores of <16.5 and >30.5 correspond to functional anosmia and normosmia, respectively (10). Subjects with a TDI score between 16.5 and 30.5 were considered to have hyposmia (11).

Translation and Scoring of ASOF

The necessary legal permission to translate the ASOF inventory to the Turkish language was obtained from Johann Lehrner by e-mail. The ASOF inventory was translated to Turkish by two independent medical translators (4). The translated inventory was approved by five ear, nose, and throat specialists who were aware of the socio-cultural properties of the study group. The Turkish version of the ASOF inventory was then retranslated to English by two independent medical translators unaware of the original ASOF inventory. A committee consisting of specialists checked the English version, and this version was resent to the authors for approval.

The original version of the ASOF consisted of three domains, including the one-item SOC, the five-item SRP, and the six-item ORQ scales. SOC indicates the olfactory performance on a Likert scale ranging from 0 to 10 (0 indicates unable to smell and 10 indicates best possible smell). An SOC score of ≤3 indicates abnormal olfactory capabilities. SRP includes five items and measures the capability of perceiving specific odors. An SRP score of ≤2.9 indicates problems in smelling odors. The six-item ORQ measures olfaction-related quality of life. Patients with ORQ score of ≤3.7 are considered to have smell-related problems in their quality of life.

In the test-retest reliability analysis, the data related to 50 individuals were analyzed through the Spearman correlation test and compared with the data obtained after 3 weeks.

To assess the validity of the Turkish version of the ASOF, its correlation with other psychometric tests, such as the 36-Item Short-Form Health Survey questionnaire (SF-36), and beck depression inventory (BDI) was analyzed.

SF-36

The SF-36 is a multi-item scale that assesses the limitations in eight health concepts, including limitations in physical and social activities, and usual role activities caused by physical or emotional problems (12,13).

J Acad Res Med 2020;10(3):277-82

BDI

The BDI consists of 21 self-scored items that evaluate key symptoms of depression. Scores between 10 and 16, between 17 and 23, and ≥24 indicate mild, moderate, and severe depression, respectively (14,15).

Statistical Analysis

All analyses were performed using SPSS v21 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used to test data distribution. Descriptive data were expressed as mean ± standard deviation, and categorical variables were presented as frequency and percentages. The Cronbach alpha coefficient was calculated to assess the internal consistency of the ASOF and its subscales. The test-retest reliability was calculated by correlating initial and subsequent test scores based on the Spearman correlation coefficient.

The convergent validity of the ASOF and its subscales was assessed by correlating their scores with SF-36 and BDI using the Spearman's rank coefficient of correlation. The discriminative validity of the ASOF was evaluated by comparing its scores between subgroups of patients with anosmia, hyposmia, and normosmia by using the Kruskal-Wallis test. The correlation of the ASOF with TDI score and its subscales (T, D, and OI) was evaluated using the Spearman's rank correlation coefficient. The association of the ASOF subtests with patients' sex and age was also examined using the Mann-Whitney U Test and Spearman's rank correlation coefficient, respectively. Two-tailed $p<0.05$ was accepted as statistically significant.

RESULTS

The study enrolled 133 subjects (mean age: 44.83±13.15 years), 46.5% of the subjects were men. Hyposmia and anosmia were noted in 54 (48.2%) and 58 (51.8%) participants. The control groups consisted of 21 healthy volunteers. The etiology was chronic rhinosinusitis, allergic rhinitis, post-upper respiratory tract infection, and post-traumatic in 29 (25.9%), 24 (21.4%), 42 (37.5%), and in 17 (15.2%) subjects, respectively. The duration of olfactory loss was 29.71±9.92 months.

The Cronbach α coefficients calculated for the ASOF-SRP and ASOF-ORQ in all patients were 0.98 and 0.97, with relatively high internal consistency, respectively.

The test-retest reliability coefficient for subscales were 0.97 ($p<0.001$) and 0.94 ($p<0.001$) for ASOF-SRP and ASOF-ORQ, respectively.

For validation, we assessed both convergent and discriminant validity. The convergent validity of the ASOF subscales (SOC, SRP, and ORQ) were assessed by correlating their scores with other validated psychometric tests. ASOF-SOC, ASOF-SRP, and ASOF-ORQ showed significant positive correlations with all SF-36 score and SF-36 domains, and negative correlations with BDI (Table 1). The discriminant validity of the ASOF was evaluated by comparing ASOF-SOC, ASOF-SRP, and ASOF-ORQ scores in patients with different olfactory functions (anosmia, hyposmia, and normosmia). ASOF-SOC, ASOF-SRP, and ASOF-ORQ scores in healthy controls were significantly higher than those in patients with hyposmia and anosmia ($p=0.001$). ASOF-SOC, ASOF-SRP, and ASOF-ORQ scores in patients with hyposmia were also higher than those in patients with anosmia ($p=0.001$) (Table 2, Figure 1). In addition, all SF-36 domain scores in healthy controls were higher than those in patients with hyposmia and anosmia ($p<0.001$). Moreover, the BDI score in healthy controls was significantly lower than that in patients with hyposmia and anosmia ($p<0.001$).

Statistically significant negative correlations of T, D, OI, and TDI scores with the BDI score and statistically significant positive correlations of T, D, OI, and TDI scores with each of the SF-36 domains and overall SF-36 scores were noted. TDI score and its subscales (T, D, and OI) were also positively correlated with ASOF-SOC, ASOF-SRP, and ASOF-ORQ scores (Table 3). However, no significant correlations were observed between age and ASOF-

Table 1. Correlation between ASOF test with SF-36 and BDI

	ASOF-SOC		ASOF-SRP		ASOF-ORQ	
	r	p	r	p	r	p
PF	0.620	<0.001	0.454	<0.001	0.445	<0.001
RP	0.542	<0.001	0.409	<0.001	0.423	<0.001
RE	0.622	<0.001	0.513	<0.001	0.432	<0.001
VT	0.699	<0.001	0.658	<0.001	0.655	<0.001
MH	0.643	<0.001	0.572	<0.001	0.559	<0.001
SF	0.603	<0.001	0.604	<0.001	0.595	<0.001
BP	0.696	<0.001	0.703	<0.001	0.722	<0.001
GH	0.702	<0.001	0.601	<0.001	0.639	<0.001
BDI	-0.634	<0.001	-0.585	<0.001	-0.564	<0.001

ASOF: assessment of self-reported olfactory functioning and olfaction-related quality of life, ASOF-SOC: self-reported capability of perceiving specific odors scale, ASOF-SRP: self-reported capability of perceiving specific odors scale, ASOF-ORQ: self-reported olfaction related quality of life, SF-36: 36-Item Short-Form Health Survey, PF: physical functioning, RP: role limitation due to physical health, RE: role limitations due to emotional problems, VT: vitality, MH: mental health, SF: social function, BP: bodily pain, GH: general health perception, BDI: beck depression inventory

Table 2. Comparison of ASOF scores between healthy control and patients with hyposmia and anosmia

	Healthy controls (n=21)	Patients with hyposmia (n=54)	Patients with anosmia (n=58)	p^1	p^2	p^3
ASOF-SOC	7.62±0.8	2.85±1	1.84±1.02	<0.001	<0.001	<0.001
ASOF-SRP	4.93±0.22	2.8±0.56	2.06±0.48	<0.001	<0.001	<0.001
ASOF-ORQ	4.93±0.23	2.77±0.53	2.6±0.33	<0.001	<0.001	<0.001

Data expressed as mean ± standard deviation.
ASOF-SOC: self-reported capability of perceiving specific odors scale, ASOF-SRP: self-reported capability of perceiving specific odors scale, ASOF-ORQ: self-reported olfaction related quality of life, p^1: control group vs group with hyposmia (p=0.001; p<0.01), p^2: control group vs group with anosmia (p=0.001; p<0.01), p^3: groups with hyposmia vs anosmia (p=0.001; p<0.01)

Table 3. Correlation of ASOF test, SF-36 test and BDI test with olfactory tests (TDI score and its subtests OT, OD, and OI)

	T		D		OI		TDI	
	r	P	r	p	r	p	r	p
ASOF-SOC	0.813	<0.001	0.820	<0.001	0.827	<0.001	0.843	<0.001
ASOF-SRP	0.808	<0.001	0.841	<0.001	0.808	<0.001	0.846	<0.001
ASOF-ORQ	0.699	<0.001	0.728	<0.001	0.665	<0.001	0.715	<0.001
PF	0.535	<0.001	0.505	<0.001	0.497	<0.001	0.513	<0.001
RP	0.499	<0.001	0.433	<0.001	0.421	<0.001	0.456	<0.001
RE	0.522	<0.001	0.523	<0.001	0.547	<0.001	0.541	<0.001
VT	0.639	<0.001	0.606	<0.001	0.644	<0.001	0.648	<0.001
MH	0.543	<0.001	0.495	<0.001	0.498	<0.001	0.505	<0.001
SF	0.549	<0.001	0.598	<0.001	0.556	<0.001	0.587	<0.001
BP	0.646	<0.001	0.653	<0.001	0.592	<0.001	0.634	<0.001
GH	0.633	<0.001	0.602	<0.001	0.592	<0.001	0.617	<0.001
BDI	-0.588	<0.001	-0.536	<0.001	-0.521	<0.001	-0.556	<0.001

ASOF: assessment of self-reported olfactory functioning and olfaction-related quality of life, ASOF-SOC: self-reported capability of perceiving specific odors scale, ASOF-SRP: self-reported capability of perceiving specific odors scale, ASOF-ORQ: self-reported olfaction related quality of life, SF-36: 36-Item Short-Form Health Survey, PF: physical functioning, RP: role limitation due to physical health, RE: role limitations due to emotional problems, VT: vitality, MH: mental health, SF: social function, BP: bodily pain, GH: general health perception, BDI: beck depression inventory, T: odor threshold, D: odor discrimination, OI: odor identification

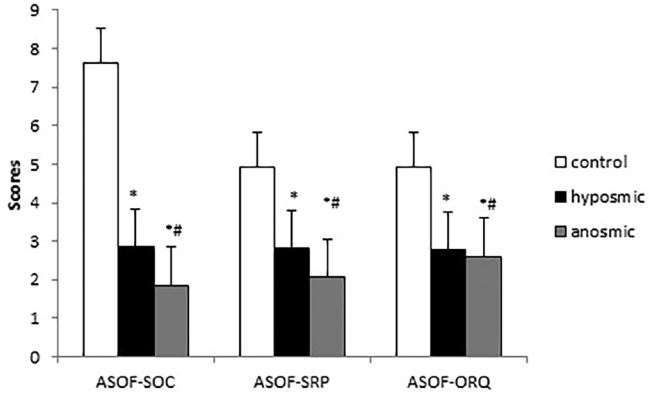

Figure 1. Comparison of ASOF scores between healthy control and patients with hyposmia and anosmia

*p<0.05 in comparison of the control group vs. the groups with hyposmia and anosmia, #p<0.05 in comparison of the groups with hyposmia vs anosmia, ASOF: assessment of self-reported olfactory functioning and olfaction-related quality of life, ASOF-SOC: self-reported capability of perceiving specific odors scale, ASOF-SRP: self-reported capability of perceiving specific odors scale, ASOF-ORQ: self-reported olfaction related quality of life

SOC, ASOF-SRP, and ASOF-ORQ scores (p=0.773; p=0.60; p=0.921, respectively). ASOF-SOC, ASOF-SRP, and ASOF-ORQ scores were also similar in male and female participants (p=0.347; p=0.268; p=0.435, respectively).

DISCUSSION

This study showed that the Turkish version of the ASOF is highly reliable and valid to assess the subjective severity of OD in a Turkish population. The Cronbach α coefficients calculated for the ASOF-SRP and ASOF-ORQ in all patients were 0.98 and 0.97, respectively. The test-retest reliability for subscales also ranged between 0.94 and 0.97, suggesting that the ASOF has high reproducibility. Thus, test-retest reliability was found to be acceptable for ASOF. The significant correlations between ASOF-SOC, ASOF-SRP, and ASOF-ORQ with overall SF-36 score and SF-36 domains, and significant negative correlations between ASOF-SOC, ASOF-SRP, and ASOF-ORQ with BDI showed the convergent validity of the ASOF subscales. ASOF-SOC, ASOF-SRP, and ASOF-ORQ scores differed significantly among healthy

J Acad Res Med 2020;10(3):277-82

controls and patients with hyposmia and anosmia, indicating discriminant validity of the ASOF subscales. TDI score and its subscales (T, D, and OI) showed significant negative correlations with the BDI score and significant positive correlations with each of the SF-36 domains and overall SF-36 scores.

Because the sense of smell is associated with several biological functions, including eating, reproduction, and avoidance of danger, OD leads to difficulties in daily living. Patients with severe hyposmia or anosmia have been shown to encounter significant impairment in health-related quality of life (16). Retrospective data has revealed that patients with OD are subject to reduced body weight, appetite, and psychological well-being, as well as an increased rate of depression (17).

Several olfaction-specific psychometric assessment tools have been developed to address the impact of OD on daily life. Present Odor Perception Scale, which consists of three questions aiming to identify how well patients think they can smell, is one of the earliest questionnaires used for this purpose (18). QOD is another widely used psychometric assessment tool utilized to assess the quality of life related to OD (6). However, shortness of psychometrically validated instruments concerning self-reported general olfactory capability, self-reported capability of reporting specific odors and self-reported olfaction-related quality of life in patients with OD led to the development of novel psychometric assessment tools, such as the ASOF.

The ASOF has been shown to have excellent psychometric properties in addition to being easy to use in clinical practice. Therefore, the validity and reliability of the Turkish version of the ASOF were assessed for its application in subjects with OD. Our findings indicate that Turkish version of the ASOF is highly valid for assessment of the self-reported olfaction-related quality of life. The validity was assessed using both discriminant and convergent techniques. Discriminant validity was analyzed to determine the ASOF's discriminative power by comparing the ASOF score between healthy controls and patients with OD. Significant differences were found in ASOF-SOC, ASOF-SRP, and ASOF-ORQ scores among participants with normosmia, hyposmia, and anosmia. These results support the findings published by Pusswald et al. (4), which showed significant differences in ASOF-SOC, ASOF-SRP, and ASOF-ORQ between subjects with OD and healthy controls. This finding suggests that the Turkish version of the ASOF might be a valuable tool for discrimination of subjects with hyposmia from those with anosmia and subjects with hyposmia from those with normal olfactory function. Convergent validity was evaluated through correlation of the ASOF to Sniffin' Sticks test by using the data of the patients with OD. The TDI overall score and its subscales (T, D, and OI) had significant positive correlations with all ASOF subtests. The convergent validity of the Turkish version of the ASOF was also assessed by correlating ASOF subtest scores with other validated and commonly used psychometric tests, including SF-36 and BDI, which measure similar or related concepts. ASOF subtests displayed significant positive correlations with overall SF-36 score and SF-36 domains, and negative correlations with BDI. Finally, the relation of the ASOF scales with age and sex in patients with OD was also investigated. The Turkish version of the ASOF was found to have no relation to age or sex.

Study Limitations

This study has limitations. Subjects with qualitative smell disorders, such as parosmia and phantosmia, were not enrolled in the study. Further studies enrolling patients with these disorders can further demonstrate the validity of the Turkish version of the ASOF in a larger population with OD. Nevertheless, given the high internal consistency and discriminant and convergent validity, we suggest that the Turkish version of the ASOF is highly valid and reliable to demonstrate subjective OD.

CONCLUSION

This study shows that the Turkish version of the ASOF is a reliable and valid measure to determine the impairment in daily life associated with OD. Its cost effective and easy-to-use feature makes the ASOF a useful tool for initial assessment and follow-up of patients with OD.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Medipol University (approval number: 268, date: 22.03.2019).

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Relationship of Endometrial Polyp Prediction with Clinical and Demographic Findings

Dilşad Herkiloğlu[1], Şefik Gökçe[1], Pınar Göksedef[1], Canan Kabaca[2], Gülhan Sağıroğlu[2]

[1]Yeni Yüzyıl University, Private Gaziosmanpaşa Hospital, Clinic of Gynecology and Obstetrics, İstanbul, Turkey
[2]University of Health Sciences Turkey, Zeynep Kamil Gynecology and Child Diseases Training and Research Hospital, Clinic of Gynecology and Obstetrics, İstanbul, Turkey

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ABSTRACT

Objective: Endometrial polyp (EP) can be diagnosed clinically by transvaginal ultrasonography (TVUSG). In our study, we aimed to show the effectiveness of TVUSG in detecting EP with the hysteroscopy (H/S) results of patients who applied to our clinic and were considered for EP in TVUSG.

Methods: One hundred twenty-five patients who were admitted to the obstetrics outpatient clinics of our hospital between August 1, 2015 and April 1, 2017 and were scheduled for H/S operation with a pre-diagnosis of EP were included in the study. The relationship between the age, abnormal uterine bleeding (AUB), infertility history, and the presence of EP after H/S was examined in the patients who had EP appearance on ultrasonography. The H/S results of patients with suspected EP in TVUSG and the efficiency of TVUSG in detecting EP were investigated.

Results: The average age of the patients was 38.04±8.47 and ranged from 21 to 63. A significant difference was found in H/S between the ages of those with polyps and those without them (p=0.012). In patients with polyps in H/S, the average endometrium thickness was 13.36±5.37 mm, and in non-polyps, endometrium thickness was 14.08±4.58 mm. There was no significant difference in terms of endometrial thickness (p=0.141). The rate of AUB history (34.5%) in those with polyps seen in H/S was significantly higher than the rate of AUB history (13.2%) in those without polyps (p=0.007). Polyps were observed in H/S in 76% of 73 cases aged >35, and this rate was found to be significantly higher than cases under 35 years old. The sensitivity and negative predictive value was the highest in the diagnosis of polyp in the case of >35 years old alone (64.3% and 76.7%, respectively); Specificity and positive predictive value were the highest in both AUB and >35 years of age (89.4% and 85.7%, respectively).

Conclusion: With TVUSG, the diagnosis of EP can be made with high accuracy in the presence of over 35 years of age with AUB findings.

Keywords: Hysteroscopy, endometrial polyp, abnormal uterine bleeding

ORCID IDs of the authors: D.H. 0000-0001-9915-3469; Ş.G. 0000-0003-0939-4539; P.G. 0000-0002-2163-6329; C.K. 0000-0002-7069-279X; G.S. 0000-0002-0334-1260.

Corresponding Author: Dilşad Herkiloğlu,
E-mail: dilsadherkiloglu@hotmail.com

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INTRODUCTION

Endometrial polyps (EP) are benign lesions that rarely show malignancy, resulting from hyperplasia of the endometrial gland and stroma. Although it is seen at all ages, it is most often observed in women between the ages of 40-55. EP is diagnosed in patients as a result of complaints of menometroragia, pelvic pain, infertility and perimenosal vaginal bleeding (1).

The prevalence of EP ranges from 7.8% to 34.9%, depending on the population studied (2,3). Intrauterine evaluation is performed by ultrasonography, hysterosalpingography, saline infusion sonography (SIS), hysteroscopy (H/S) and magnetic resonance imaging. Transvaginal ultrasonography (TVUSG) is a method with high accuracy for the uterine cavity (4,5). Although SIS has a higher diagnostic rate, patients can ultimately be referred to H/S (6). The improved diagnostic accuracy of the polyp by various methods has led to the increase in the use of H/S, which proves the best diagnosis and treatment approach.

We aimed to show the efficacy of TVUSG in detecting EP by examining the relationship between the presence of EP after (H/S) in patients with abnormal uterine bleeding (AUB), a history of infertility and EP appearance on ultrasonography.

METHODS

One hundred twenty-five patients who were admitted to the obstetrics outpatient clinics of our hospital between August 1, 2015 and April 1, 2017 with a pre-diagnosis of EP and scheduled for H/S operation were included in the study. Patients with complaints of deterioration in their previous menstrual pattern, sudden increase in the number of pads they used during the day, 3 or more days of deviation from normal menstruation periods, and a change of 4 days or more between menstruations were evaluated as AUB. Endometrial thickness was evaluated with a voluson GE brand 4-8 mHz wide-band Vaginal Probe in any phase of the menstrual cycle. With TVUSG, external-external measurements were made from the endometrium and myometrium border passing through the midline of the uterus in the sagittal plan, including the anterior and posterior layers, without including fluid deposits in the cavity. If the endometrium is seen to be thickened in a certain cross section, more hyperechogenic than normal endometrium and focal thickness increases that do not exceed the junction of the endometrium and myometrium, this situation is defined as the presence of polyps in the endometrial cavity. H/S indication was given to patients with suspected polyp. Age, gravida, parity and endometrium thickness of patients were retrospectively scanned from their files. All patients were given general anesthesia between the 6th and 12th days of the cycle, and after cervical dilation in the lithotomy position, 90° loop electrodes were entered into the uterine cavity with hysteroscope. Cervical canal, cavity and both tubal ostium were examined. All the polyps that were monitored were resected and sent to pathology. Postoperative complications did not develop in patients undergoing surgery. The study was approved by the University of Health Sciences Turkey, Zeynep Kamil Obstetrics and Pediatrics Training and Research Hospital Clinical Research Ethics Committee (approval number: 89, date: 21.04.2017). Informed consent was obtained from each patient before the study.

Statistical Analysis

SPSS 24.0 (IBM Corporation, Armonk, New York, United States) program was used to analyze the variables. The suitability of the data for normal distribution was evaluated by the Shapiro-Wilk test, and the homogeneity of variance was evaluated by the Levene test. The Independent Samples t-test was used with Bootstrap results, while the Mann-Whitney U test was used with the Monte-Carlo simulation technique to compare groups with and without polyps in H/S with each other according to quantitative data. Pearson chi-square tests, Monte-Carlo Simulation technique and Exact results were used in comparing those with and without polyps in H/S with each other according to categorical variables, and the column ratios were compared with each other and expressed according to the Benjamini-Hochberg corrected p-value results. Sensitivity and specificity for cutoff calculated to distinguish between polyps and non-polyps in H/S by age were examined and expressed by receiver operating characteristic curve analysis. The variables were examined at 95% confidence order, and p-value less than 0.05 was considered significant.

RESULTS

The study included 125 patients. Demographic characteristics of patients are shown in Table 1. The average age of the patients was 38.04±8.47 and ranged from 21 to 63. AUB was present in 28% of cases. The rate of cases diagnosed with infertility was 22.4% (n=22). In the study of pathology results of 125 patients, endometrial hyperplasia was observed on the ground of EP in only 1 of them.

The number of polyps in H/S was 87 (69.9%). The average age of 87 patients who were monitored for polyps in H/S was 39.25±8.27, and the average age of 38 patients who were not monitored for

Table 1. Demographics

	n=125, (%)
Age (mean ± SD)	38.04±8.47
Endometrium thickness (mm)	13.45±0.25
Gravida median (range)	2 (0-12)
Parity median (range)	1 (0-11)
Living median (range)	1 (0-11)
Presence of AUB	35 (28%)
Infertility	28 (22.4%)
Presence of polyp	87 (69.9%)

SD: standard deviation, AUB: abnormal uterine bleeding

J Acad Res Med 2020;10(3):283-87

polyps was 35.26±8.36. A significant difference was found in H/S between the ages of those with polyps and those without them (p=0.012). In patients with polyps in H/S, the average endometrium thickness was 13.36±5.37 mm, and in non-polyps, endometrium thickness was 14.08±4.58 mm. No significant differences were found in endometrium thickness (p=0.141).

In 30 of the 35 patients with AUB, EP was monitored at H/S. AUB history rate (34.5%) was significantly higher in those who showed polyps in H/S than in those who did not show polyps (13.2%) (p=0.007). In 76% of 73 cases with an age of >35, polyps were monitored at H/S, and this rate was significantly higher than in cases under the age of 35. The incidence of polyps in patients with suspected EP and infertility in TVUSG was not monitored differently from others (p=0.467 and 0.246, respectively) (Table 2). In 28 (22.4%) of cases, both AUB and >35 years of age were present. AUB complaint and the simultaneous presence of >35 years of age were significantly associated with the presence of polyps compared to others (p=0.035).

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) values in polyp diagnosis of the presence of AUB, >35 years of age and both at the same time are summarized in Table 3. Only >35 years of age was the highest sensitivity and NPV in the diagnosis of polyps (64.3% and 76.7%, respectively); specificity and PPV were the highest if both AUB and >35 years of age (89.4% and 85.7%, respectively).

DISCUSSION

EP is a focal hyperplastic growth of the endometrial glands and stroma. AUB is the most common finding in age groups of reproductive age and postmenopausal age group (2). In many previous studies, H/S has been shown as the gold standard diagnostic and treatment method in patients with AUB (7,8). Similarly, in our study, the rate of AUB history in those with polyps in H/S was found to be significantly higher than the rate of AUB history in those without polyps. In addition to being therapeutic, H/S has become superior to other methods when evaluated in terms of affecting quality of life and cost.

TVUSG can be considered as a first-line examination method by its two-dimensional imaging of the uterine cavity. But it should be considered that it has noticeably poor sensitivity and specificity compared to SIS. The effectiveness of SIS in the diagnosis of focal lesions increases by imaging both the uterine cavity and myometrium. SIS stands out compared to H/S, which is an invasive procedure, due to its easy applicability, tolerability, low cost and outpatient applicability. H/S is the gold standard in the pathologies of the uterine cavity in all imaging methods, including SIS, as it allows the treatment of detected lesions in the same session, even if it is considered an alternative to H/S. Ragni et al. (6), in their study including 98 infertile patients, took H/S as the gold standard and compared SIS with TVUSG. At the end of the study, they reported that SIS has a higher diagnostic rate than TVUSG in intrauterine pathologies. When compared with H/S, the sensitivity of SIS was 98% and specificity was 95%, and the sensitivity of TVUSG was 91% and specificity was 83%. Due to the low diagnostic values of SIS in lesions such as endometrial hyperplasia, endometrial cancer and endometritis, histopathological diagnosis with endometrial biopsy is required in suspicious cases.

TVUSG is recommended to be used for pre-evaluation in patients with AUB (7). However, it has been observed that 24% of polyps can be missed with TVUSG (8). In our study, the rate of polyp incidence as a result of H/S performed on patients with a clinical diagnosis of EP in TVUSG was observed as 69.6%. Demirtaş et al. (9) confirmed the diagnosis of EP in 95 (70.9%) of 130 patients with a pre-diagnosis of EP, by performing H/S and dilatation and

Table 2. Distribution of endometrial polyps by clinical and demographic data

Polyp in hysteroscopy	No 38 (30.4%)	Yes 87 (69.6%)	Total 125 (100%)	p
Age >35	17 (23.3)	56 (76.6)	73 (58.4)	0.041
AUB	5 (14.3)	30 (85.7)	35 (28.0)	0.007
Polyp suspicion at USG	11 (26.2)	31 (73.8)	42 (33.6)	0.467
History of infertility	11 (39.2)	17 (69.6)	28 (22.4)	0.246
AUB and age >35	24 (14.3)	4 (85.7)	28 (22.4)	0.035

AUB: abnormal uterine bleeding, USG: ultrasonography

Table 3. presence of AUK, >35 years of age and simultaneous values of both in polyp diagnosis

	Sensitivity	Specificity	PPV	NPV
AUB	34.4%	86.8%	85.7%	36.6%
Age >35	64.3%	55.2%	76.7%	40.3%
AUB and age >35	27.5%	89.4%	85.7%	35.1%

AUB: abnormal uterine bleeding, PPV: positive predictive value, NPV: negative predictive value

curettage. In our study, although the diagnosis was confirmed only by H/S, we attribute our lower rates to TVUSG quality and operator differences in the pre-diagnosis evaluation.

In a metaanalysis covering 51 studies on the malignancy potential of EP, malignancy rates in EP were found to be 0-15% (10). In a study associated with EP and malignancy, 516 EP were excised with H/S and histopathologically 96.9% were benign, 1.2% were premalignant, and 1.9% were malignant (11). In our study, we did not observe malignancy in the histopathological diagnosis, only one patient had endometrial hyperplasia. Since endometrial hyperplasia is considered as a premalignant lesion, we found similar rates in our study.

The prevalence of EP increases with age. In the study of Ricciardi et al. (12), 79.8% of women were under 60 years old. In the practical report of the American Association of Gynecological Laparoscopists, it was stated that increasing age is a risk factor for EP (13). In our study, polyps were monitored at H/S in 76% of 73 cases with an age of >35, and this rate was significantly higher than in cases under the age of 35 (p=0.041). Only >35 years of age was the highest sensitivity and NPV in the diagnosis of polyps (64.3% and 76.7%, respectively); specificity and PPV were the highest if both AUB and >35 years of age (89.4% and 85.7%, respectively). Thus, when this age group applies to gynecology clinics, the possibility of diagnosing EP increases, but it will save time for diagnosis and treatment.

In a study by Hassa et al. (14), 29.2% of the patients had multiple polyp, and in another study by Arıcı et al. (15), it was found that the number, location, and size of the polyps were not related to the patients' findings. In a study conducted by Preutthipan and Herabutya (16), the average size of the polyp in premenopausal women was 3.4±0.9 cm, and it was found to be 2.5±0.8 cm smaller than postmenopausal women. When the polyp area was examined, the right or left sidewalls, common locations, followed by the anterior and posterior walls. This situation can be considered as one of the causes of infertility in women with polyps that obstruct tubal osteosis. EP can cause infertility, especially in the cornual area. In our study, no statistically significant relationship was found between infertility and polyps in H/S (p=0.246). However, EP was monitored in 17 (69.6%) of 28 patients who were infertile. In the study of Shokeir et al. (17), EPs were diagnosed hysteroscopically in 4% of all women with unexplained infertility and 14.8% of infertile women with amenorrhea. We can attribute our higher rate to a small number of patients admitted to a gynecology clinic. As a result, successful results can be achieved for infertile patients with H/S, which is more convenient in terms of time and cost.

CONCLUSION

AUB is the most common symptom in patients monitored by EP. EP can be diagnosed with high accuracy if they are over 35 years of age and have a combination of AUB findings. Although H/S is the most valuable diagnostic and treatment method in EP diagnosis, TVUSG should be the first option for preliminary evaluation in terms of cost and convenience.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Zeynep Kamil Obstetrics and Pediatrics Training and Research Hospital Clinical Research Ethics Committee (approval number: 89, date: 21.04.2017).

Informed Consent: Informed consent was obtained from each patient before the study.

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Comparative Evalaution of the Effects of Short-Wave Diathermy, Ultrasound, and TENS on Pain and Physical Functions in Knee Osteoarthritis

Betül Başar[1], Belgin Erhan[2]

[1]University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Turkey
[2]İstanbul Medeniyet University, Göztepe Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Turkey

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ABSTRACT

Objective: Short-wave diathermy (SWD), ultrasound (US), and Transcutaneous Electrical Nerve Stimulation (TENS) are commonly used agents in physical therapy treatments. This study aimed to evaluate the therapeutic effects of these physical therapy agents in women with bilateral knee osteoarthritis (OA).

Methods: Three equal groups of 60 women diagnosed with knee OA of age 45-65 years based on their treatment regimens were created: SWD (group 1), US (group 2), and TENS (group 3). These patients had stages 2 and 3 knee OA with reference to the Kellgren-Lawrence Classification System. The evaluations were performed using the visual analog scale (VAS) and Western Ontorio and McMaster Universities Osteoarthritis Index (WOMAC) and the physical function tests at the time points of pre-treatment, post-treatment, and 1-month follow-up duration.

Results: There were not any significant difference among the groups in terms of age, height, weight, body mass index, duration of pain, and radiological staging of OA. All 3 physical therapy agents were effective in terms of pain and physical functions. Better results were obtained in terms of the VAS and WOMAC scores at post-treatment and at 1-month follow-up when compared to that at pre-treatment assessment. However, comparison of the results of all 3 physical therapy agents showed that TENS treatment was more effective in relieving pain. Although no significant difference was noted among the groups in terms of the physical functions, SWD was more effective in terms of the scores of repeated sit-to-stand test and 20 m walk tests, while US was more effective in terms of the straight-line walk test scores.

Conclusion: Treatment with the physical therapy agents was effective in alleviating the physical functions. In addition, TENS was found to be more effective in alleviating pain.

Keywords: Short wave diathermy, ultrasound, TENS, pain, physical functions

ORCID IDs of the authors: B.B. 0000.0003.3547.2537; B.E. 0000.0019.8675.8493.

Corresponding Author: Betül Başar,
E-mail: betulakarvardar@hotmail.com

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INTRODUCTION

Osteoarthritis (OA) may affect several joints, especially the weight-bearing joints (1). The knee is the most commonly affected joint in OA. The prevalence of OA is 12%-35% in the general population (2,3). OA causes pain, joint swelling, stiffness, instability, and muscle weakness in the joints. These undesirable effects together decrease the quality of life of the patients. The aim of treatment in this situation is targeted at reducing the pain and joint stiffness, maintaining or regaining the joint range of motion and muscle strength, and reducing the dependency on daily living activities. Different physical therapy agents are frequently used for this purpose, including the most common used ones of short-wave diathermy (SWD), Transcutaneous Electrical Nerve Stimulation (TENS), and ultrasound (US) (4).

SWD is an electrotherapeutic modality applied in the treatment of knee OA. In this treatment module, the application of continuous electromagnetic radiation increases the tissue temperature, which in turn induces vasodilatation, reduces muscle spasms, accelerates the cellular activity, and elevates the pain threshold (5).

High-frequency sound waves are applied to the affected tissues during US therapy. US therapy enhances soft tissue healing, decreases the inflammatory response, increases the blood flow, increases the metabolic activity, and decreases pain (6).

The efficiency of different electrical characteristics of TENS is to selectively activate different types of fiber. The aim of conventional TENS is to selectively activate Aβ afferents, producing segmental analgesia (7).

There are different theories about the mechanism of TENS. Most researchers agree that this device is effective in relieving pain using the 2 mechanisms of gate control and secretion of endorphins (8).

In this prospective study, we investigated the effects of SWD, US, and TENS treatments on the pain and physical functions. Accordingly, we evaluated the effects of SWD, US, and TENS treatments on the pain and physical functions in patients with OA.

METHODS

The patients receiving SWD, US, and TENS treatments with the diagnosis of knee OA were reviewed prospectively during February 2008-2009. The scores of complete visual analogue scale (VAS), Western Ontario and McMaster University Osteoarthritis Index (WOMAC), lift test, pick-up test, repeated sit-to-stand test, sock test, stair ascending and descending test, straight-line walking, timed up & go test, and 20 m walk test of 20 patients from each group were analyzed at pre-treatment, post-treatment, and 1-month follow-up.

Ethics committee approval was obtained from the Local Ethics Committee of the İstanbul Physical Therapy and Rehabilitation Training and Research Hospital in January 2008. Written informed consent, approved by our institutional review board, was obtained from all patient.

Female patients aged 45-65 years with bilateral knee OA were included in the study. Patients with a history of previous knee joint surgery, intra-articular injection, and lower back or hip pain in addition to knee pain were excluded from the study. Bilateral knee OA was diagnosed with reference to the American College of Rheumatology criteria. These patients had stages 2 or 3 knee OA according to the Kellgren-Lawrence Classification System. Twenty patients each were grouped as follows: group 1: patients receiving SWD treatment, group 2: patients receiving US therapy, and group 3: patients receiving TENS treatment (9).

SWD was applied for 15 min, US (1 MHz, 1.5 W/cm^2 dose) for 5 min, and TENS for 20 min in each session. Each patient received a total of 15 sessions of the prescribed treatment.

In each group, isometric quadriceps strengthening exercise was applied as a home program. Patients performed this exercise program for 3 months, thrice a day for 1 h at each session.

Evaluations were made in terms of recording the scores of VAS, WOMAC, and physical function tests at the pre-treatment, post-treatment, and 1-month follow-up (10).

Physical functions were evaluated using the lift test, pick-up test, repeated sit-to-stand test, sock test, stair ascending and descending test, stair ascending and descending test, straight-line walking, timed up & go test, and 20-m walk test (11-13).

Statistical Analysis

SPSS for Windows 13.0 package program was applied for statistical analysis. Chi-square test was used to compare the demographic ratios among the groups, and the analysis of variance test was applied to compare the means among the groups. Mann-Whitney-U test or Wilcoxon test were used to compare the non-parametric tests. Statistical significance was accepted as $p<0.05$.

RESULTS

No significant difference was found among the groups in terms of age, height, weight, body mass index, duration of pain, and radiological staging of OA ($p>0.05$) (Table 1).

SWD Treatment Group

VAS score: Post-treatment value was significantly lower than the pre-treatment value ($p=0.001$). At the 1-month follow-up, the VAS score was significantly lower than that at the post-treatment assessment ($p=0.001$) (Table 2).

Physical functional tests: The post-treatment and 1-month follow-up values were significantly better than the pre-treatment value ($p<0.001$). There was no significant difference between the values of 1-month follow-up and that at post-treatment ($p>0.05$) (Table 2).

WOMAC pain: The post-treatment value was significantly lower than the pre-treatment one ($p=0.001$). At the 1-month follow-up, the WOMAC Pain score was significantly lower than the post-treatment score ($p=0.003$) (Table 2).

Table 1. Comparison of groups in terms of age, height, weight, BMI, duration of pain, and radiological grading

	Group 1 SWD	Group 2 US	Group 3 TENS	p
Age (year)	55.15±6.61	54.75±6.12	55.20±5.32	0.87
Height (cm)	158.30±6.82	162.00±6.68	160.45±5.35	0.22
Weight (kg)	78.35±12.70	79.45±14.39	75.55±10.14	0.30
BMI (kg/cm^2)	29.66±9.25	30.80±5.53	29.57±5.06	0.66
Duration of pain (month)	23.20±13.92	16.26±9.34	18.30±10.05	0.31
Kellgren-Lawrence	-	-	-	0.31
Grade 2	10	8	16	-
Grade 3	30	32	24	

BMI: body mass index. SWD: short-wave diathermy, US: ultrasound, TENS: Transcutaneous Electrical Nerve Stimulation

Table 2. Pre-treatment, post-treatment, and 1-month follow-up values of the patients treated with SWD

Group 1 (SWD)	Pre-treatment	Post-treatment	First month follow-up
VAS	7.45±0.99	5.40±1.09	4.60±1.09
Lift test	11.40±2.13	13.05±2.23	12,70±2.17
Pick-up test	2.15±0.67	1.75±0.78	1.76±0.67
Repeated sit-to-stand test (sn)	16.46±3.68	13.83±3.80	13.17±3.82
Sock test (0-3)	2.25±0.71	1.80±0.69	1.80±0.69
Stair ascending test (sn)	13.79±4.06	11.06±4.08	10.31±3.88
Stair descending test (sn)	13.72±4.33	11.23±4.50	11.15±4.32
Straight-line walking (sn)	16.38±5.24	14.51±5.24	14.44±5.17
Timed up & go test (sn)	12.31±3.22	9.91±2.75	9.92±2.65
Twenty meter walk test (sn)	20.36±4.26	18.12±3.18	17.61±2.86
WOMAC pain	14.80±2.82	10.85±2.66	10.00±2.90
WOMAC stiffness	5.10±1.11	3.70±1.30	3.25±1.25
WOMAC physical function	50.70±4.90	38.80±8.28	39.50±9.29
WOMAC total	70.60±6.07	54.85±11.37	51.75±11.67

SWD: short-wave diathermy, VAS: visual analog scale, WOMAC: Western Ontorio and McMaster Universities Osteoarthritis Index

WOMAC stiffness: The post-treatment value was significantly lower than the pre-treatment score (p=0.002). At the 1-month follow-up, the WOMAC Stiffness score was significantly lower than the post-treatment score (p=0.02) (Table 2).

WOMAC physical function: The post-treatment and 1-month follow-up values were significantly lower than the pre-treatment value (p<0.001). No significant difference was noted between the 1-month follow-up and post-treatment assessment (p=0.41) (Table 2).

WOMAC total: The post-treatment value was significantly lower than the pre-treatment one (p=0.002). At the 1-month follow-up, the WOMAC total score was significantly decreased than that at post-treatment assessment (p=0.003) (Table 2).

US Treatment Group

VAS score: The post-treatment value was significantly lower than the pre-treatment one (p<0.001). No significant difference was noted between the 1-month follow-up and post-treatment assessment (p=0.058) (Table 3).

Physical functional tests: In the tests other than the lift test and repeated sit-to-stand test, the values at post-treatment and at 1-month follow-up were significantly better than that at pre-treatment assessment (p<0.001). No significant difference was noted between the 1-month follow-up and that at post-treatment (p>0.05) (Table 3).

Lift test: Post-treatment and 1-month follow-up values were significantly better than that the pre-treatment values (p<0.001). However, at the 1-month follow-up, the lift test score was significantly lower than that at post-treatment (p=0.011) (Table 3).

Repeated sit-to-stand test: The post-treatment and 1-month follow-up values were significantly better than that the pre-treatment value (p<0.001). However, at the 1-month follow-up, the repeated sit-to-stand test score was significantly lower than that at post-treatment assessment (p=0.038) (Table 3).

WOMAC pain, stiffness, physical function and total score: The post-treatment and 1-month follow-up values were significantly better than the pre-treatment values (p<0.001). No significant

J Acad Res Med 2020;10(3):288-93

difference was noted between the 1-month follow-up and at post-treatment assessment (p>0.05) (Table 3).

TENS Treatment Group

VAS score: The post-treatment value was significantly lower than the pre-treatment value (p<0.001). No significant difference was noted between the 1-month follow-up and post-treatment values (p=0.052) (Table 4).

Physical functional tests: In the straight-line walking test, the post-treatment and 1-month follow-up values were significantly better than the pre-treatment value (p<0.001). No significant difference was noted between the 1-month follow-up and post-treatment values (p>0.05) (Table 4).

Straight-line walking test: The post-treatment and 1-month follow-up values were significantly better than the pre-treatment value (p<0.001). However, at the 1-month follow-up, the straight-line walking test score was significantly lower than at the post-treatment assessment (p=0.04) (Table 4).

WOMAC pain: The post-treatment and 1-month follow-up values were significantly better the pre-treatment value (p<0.001). No significant difference was noted between the 1-month follow-up value and the post-treatment value (p=0.19) (Table 4).

WOMAC stiffness, physical function and total score: The post-treatment value was significantly lower than the pre-treatment

Table 3. Pre-treatment, post-treatment, and 1-month follow-up values of the patients treated with SWD

Group 2 (US)	Pre-treatment	Post-treatment	First month follow-up
VAS	7.25±0.91	4.50±1.10	4.20±0.95
Lift test	11.30±2.34	13.65±2.36	12.75±2.44
Pick-up test	1.85±0.71	1.10±0.44	1.05±0.39
Repeated sit-to-stand test (sn)	15.14±2.81	12.30±2.34	12.54±2.45
Sock test (0-3)	2.16±0.75	1.00±0.45	0.95±0.39
Stair ascending test (sn)	11.72±3.29	9.05±2.83	9.63±2.65
Stair descending test (sn)	11.33±2.59	9.30±2.15	9.50±2.15
Straight-line walking (sn)	18.27±5.74	16.23±4.28	15.88±4.33
Timed up & go test (sn)	11.22±2.39	8.91±2.08	9.26±2.27
Twenty meter walk test (sn)	19.31±4.92	17.30±6.06	16.30±7.57
WOMAC pain	13.65±2.20	9.95±2.41	9.65±2.25
WOMAC stiffness	5.20±1.50	3.55±1.09	3.30±0.97
WOMAC physical function	48.68±5.68	37.25±8.03	36.65±7.14
WOMAC total	67.75±9.17	51.00±10.84	49.60±9.25

SWD: short-wave diathermy, US: ultrasound, VAS: visual analog scale, WOMAC: Western Ontorio and McMaster Universities Osteoarthritis Index

Table 4. Pre-treatment, post-treatment, and 1-month follow-up values of the patients treated with TENS

Group 3 (TENS)	Pre-treatment	Post-treatment	First month follow-up
VAS	7.35±0.67	3.98±0.67	4.06±0.48
Lift test	13.60±2.64	14.80±3.05	14.75±3.59
Pick-up test	1.75±0.63	1.10±0.44	1.00±0.45
Repeated sit-to-stand test (sn)	14.67±2.38	12.30±2.34	11.43±2.45
Sock test (0-3)	1.65±0.58	1.00±0.45	1.05±0.39
Stair ascending test (sn)	9.75±3.03	9.05±2.83	8.41±2.49
Stair descending test (sn)	9.53±3.62	9.30±2.15	9.50±2.15
Straight-line walking (sn)	17.37±4.52	16.27±5.74	15.54±3.86
Timed up & go test (sn)	9.69±1.89	8.91±2.08	7.76±1.43
Twenty meter walk test (sn)	18.80±3.96	17.30±6.06	17.17±3.40
WOMAC pain	14.15±2.25	8.95±2.41	9.06±1.78
WOMAC stiffness	5.30±1.17	3.55±1.09	3.50±0.94
WOMAC physical function	48.40±6.72	37.25±8.03	33.95±8.88
WOMAC total	68.10±7.30	51.00±10.84	47.05±10.50

TENS: Transcutaneous Electrical Nerve Stimulation, VAS: visual analog scale, WOMAC: Western Ontorio and McMaster Universities Osteoarthritis Index

value (p<0.001). At the 1-month follow-up, the WOMAC total score was significantly decreased than that at the post-treatment assessment (p=0.001) (Table 2).

Comparison of the Groups

The VAS and WOMAC Pain scores after TENS treatment and at 1-month follow-up were better when compared to that after SWD and US treatments (p<0.05). SWD was found to be more effective in terms of repeated sit-to-stand test and 20 m walk tests after the treatment and at 1-month follow-up (p<0.05). US was most effective at 1-month follow-up in terms of the straight-line walk test scores (p<0.001). No significant difference was noted among the groups in terms of other parameters.

DISCUSSION

Our results revealed that the evaluated physical therapy agents were effective in the treatment of pain and physical functions. However, in terms of pain treatment, TENS was more effective than other agents. In terms of physical functions, SWD was more effective in terms of repeated sit-to-stand test and 20 m walk tests. According to the straight-line walk test, US is more effective.

SWD, US, and TENS are commonly used physical therapy agents applied in the treatment of knee OA. However, the effect of these physical therapy agents on joint pain remains unclear. These treatment approaches increase the temperature of the tissues on application as well as an increase in the blood flow to the tissues. As the blood flow increases, the tissue perfusion and metabolic activity also increase, and muscle relaxation is achieved (5-7). Another mechanism is called the gate control theory (5,6,14). TENS has also been reported to modulate the pain control pathway by inducing endogenous opioid secretion (15).

These physical therapy agents reduce inflammation at the joints as well as reduce the pain. The decrease in synovitis was demonstrated by a decrease in US -measured synovial tissue thickness after the treatment. Reduction in inflammation reduces pain and positively affects the range of motion of the joints (16).

Some past studies have shown that SWD, US, and TENS can reduce the pain in patients with knee OA, albeit they are insufficient in terms of the physical functions alone (16-19). It has been emphasized that exercise therapies are more important in terms of physical functions (20).

Different results on the effect of physical therapy agents on the physical functions have been reported in the literature. SWD, US, and TENS increase the compliance of patients with exercise therapy, but some studies claim that US is not as effective as SWD and TENS (21,22). On the other hand, some past studies assert that US with SWD is an effective treatment modality in the treatment of knee OA and neither are superior to each other (23,24). In another study, physical therapy agents were reported to have increased the walking distance during the treatment, although this distance decreased at the end of the treatment. In the present study, it was determined that exercise programs applied during and post-treatment could increase the walking distance during the treatment duration and prevent a decrease in the walking distance after the treatment application (21). Therefore, it is recommended to apply these physical agents together with exercise therapies for the treatment of knee OA (17,21).

In all 3 physical therapy modalities tested in this study, we found that the pain complaints decreased significantly after the treatment and at 1-month follow-up when compared to that before the treatment. On the other hand, although they were reported to be inadequate in terms of physical functions, in our study, we achieved better outcomes in terms of the scores of the physical function parameters. Furthermore, the tested physical functions did not decrease at the 1-month follow-up assessment.

Study Limitations

The absence of any control group in this study as well as the absence of medium and long-term results challenges the strengths of the study.

CONCLUSION

TENS, US, and SWD are effective interventions for the treatment of pain and physical functions in the treatment of knee OA and can thus be safely preferred as the treatment approaches. Further studies need to be conducted to investigate their effectiveness in the treatment of other joint OA.

Ethics Committee Approval: Ethics committee approval was obtained from the Local Ethics Committee of the İstanbul Physical Therapy and Rehabilitation Training and Research Hospital in January 2008.

Informed Consent: Written informed consent, approved by our institutional review board, was obtained from all patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - B.B.; Concept - B.E.; Design - B.B., B.E.; Data Collection and/or Processing - B.B.; Analysis and/ or Interpretation - B.B., B.E.; Literature Search - B.B.; Writing Manuscript - B.B.

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J Acad Res Med 2020;10(3):288-93

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T-Tube Breakage During Removal: Management by Endoscopic Retrograde Cholangiopancreatography

Mehlika Bilgi Kırmacı[1], Tamer Akay[2], Esra Özgül[3], Sezgin Yılmaz[1]

[1]Afyonkarahisar University of Health Sciences Faculty of Medicine, Department of General Surgery, Afyonkarahisar, Turkey
[2]Bandırma State Hospital, Clinic of General Surgery, Balıkesir, Turkey
[3]Afyonkarahisar University of Health Sciences Faculty of Medicine, Department of Radiology, Afyonkarahisar, Turkey

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ABSTRACT

T-tube drainage is a widely used procedure among surgeons for various biliary conditions. However, various complications may occur, especially due to the breaking-off of the T-tube from the area where it enters the common bile duct during retraction. These complications often require subsequent surgical procedures to remove the T-tube fragment from the common bile duct lumen. In selected cases, the T-tube fragment can be extracted from the common bile duct by endoscopic retrograde cholangiopancreatography (ERCP). ERCP has a life-saving role that eliminates reoperation for such a complication. Herein, we present a 42-year-old female patient who was referred to our hospital, which is as an advanced center, due to breakage during T-tube withdrawal. The patient had previously undergone open cholecystectomy and T-tube drainage. When removing the T-tube, a breakage occurred at 3-4 cm from the T-tube leg, which was left in the common bile duct. In the ERCP, the leg of the T-tube was removed from the common bile duct lumen by basket compression following endoscopic sphincterotomy and a temporary plastic stent was placed. One month after the procedure, the stent was removed with the help of the ERCP. This case is presented as a rare indication of ERCP.

Keywords: Cholangiopancreatography, endoscopic retrograde, drainage, T-tube, complications

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is widely used in the diagnosis and treatment of biliary tract and pancreatic diseases. Performed for diagnostic and therapeutic purposes, this procedure has a life-saving role in most cases. Although it is generally used for several biliary and pancreatic diseases, certain rare cases also require its use for therapeutic intentions (1). T-tube is still a matter of debate, even though Huang et al. showed in the largest meta-analysis that the insertion of a T-tube may be useful. Insertion of a T-tube reduces the incidence of biliary strictures. However, it also has adverse events, predominately leakage, peritonitis, and cholangitis. The T-tube is typically removed through the percutaneous route. However, this could be impossible, probably due to fibrotic and scarring processes. Those cases are classically treated by surgery. Endoscopic removal by ERCP is a minimally invasive approach that avoids a laparotomy (2-4). In this paper, we present a 42-year-old woman who was admitted to our ERCP unit for T-tube breakage during removal.

CASE PRESENTATION

The 42-year-old woman had undergone open cholecystectomy and T-tube drainage for biliary lithiasis at another hospital

ORCID IDs of the authors: M.B.K. 0000-0002-8034-1459; T.A. 0000-0001-8137-3658; E.Ö. 0000-0002-6005-134X; S.Y. 0000-0003-0213-3758.

Corresponding Author: Tamer Akay,
E-mail: op.dr.tamerakay@gmail.com

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40 days ago. While the surgeon was taking out the T-tube, it was broken at the junction of the head and limp. The cup part of the tube remained in the common bile duct lumen, and the patient was referred to our ERCP unit for the removal of the leg of the T-tube. The patient had a mild abdominal pain and tenderness. The biochemical parameters were in the normal range. Abdominal magnetic resonance and magnetic resonance cholangiopancreatography images revealed that the tube fragment was located in the common bile duct (Figure 1, 2).

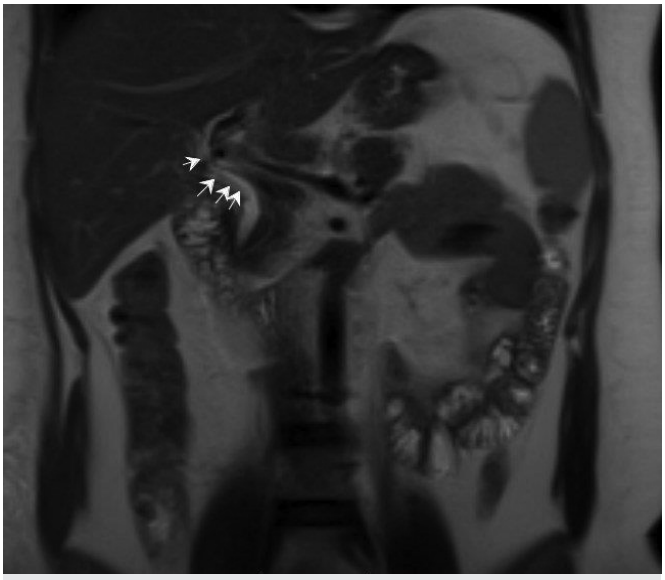

Figure 1. Coronal thin-sliced abdominal MR shows a linear filling defect extending from the distal right intrahepatic bile duct to the proximal common bile duct
MR: magnetic resonance

Figure 2. MRCP sequence shows that the common bile duct is 8 mm in diameter and that the breakage of the leg of the T-tube is in common bile duct
MRCP: magnetic resonance cholangiopancreatography

Informed consent was obtained from the patient after providing detailed information about the surgery.

ERCP was performed and the common bile duct was cannulated using a sphincterotome and guide-wire. There was a linear-tubular filling defect in the common bile duct lumen, compatible with the residual fragment of the T-tube (Figure 3). A 20 mm sphincterotomy was performed using a rounded sphincterotome and guide-wire. The common bile duct was swept using a basket. At this time, the residual fragment was extracted (Figure 4, 5).

A 10 Fr 12 cm plastic stent was placed into the common bile duct lumen. No pathologic finding was seen on control ERCP cholangiogram. A transient biliary stent was placed and the patient was discharged two days after the procedure.

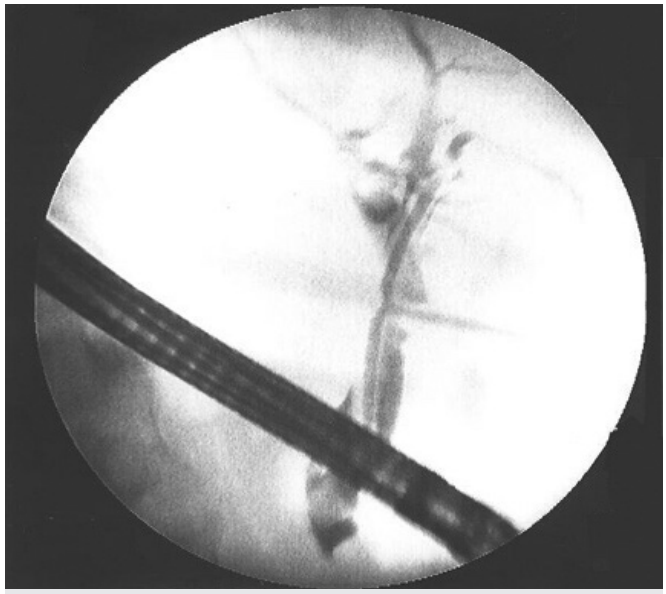

Figure 3. ERCP shows a linear-tubular filling defect in the common bile duct lumen
ERCP: endoscopic retrograde cholangiopancreatography

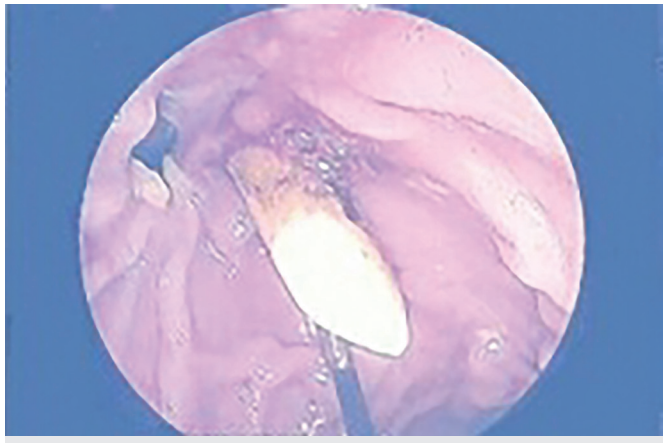

Figure 4. Endoscopic basket extraction of the residue T-tube fragment by ERCP
ERCP: endoscopic retrograde cholangiopancreatography

J Acad Res Med 2020;10(3):294-7

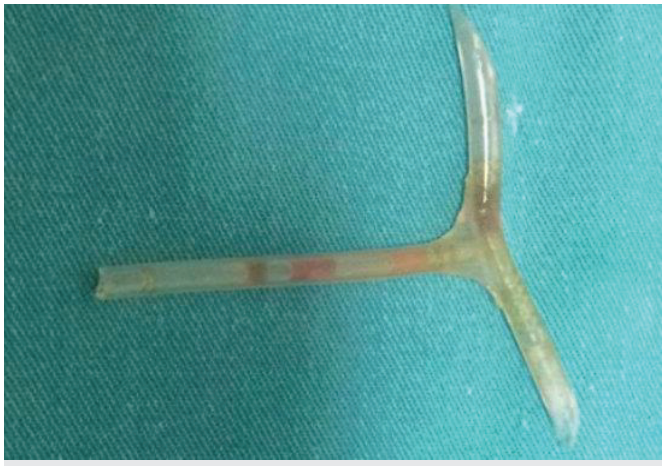

Figure 5. Retained T-tube fragment.

ERCP was successfully performed to remove the leg of the T-tube and the patient was discharged without any problem.

DISCUSSION

Common bile duct stones constitute an extended period in which ERCP is usually applied as the first-line therapy. However, ERCP cannot remove larger stones from the sphincterotomy area. Therefore, open surgery is required for such cases (5). There are several methods that can be applied during open surgery following the extraction of stones from bile ducts, such as biliary-enteric anastomosis, primary suturing of the bile duct wall and T-tube drainage.

Patients under 65 years of age who had dilated bile ducts below 15 mm in diameter are candidates for T-tube placement. The T-tube can be removed following a period of 4 days-2 weeks depending on the preference (6).

Although T-tube drainage is a commonly used procedure, it has several complications resulting in biloma, bile ascites, cholangitis, and peritonitis. These complications may occur due to bile leak following T-tube removal. In addition, there are other rare complications that occur during the accidental breakage from the insertion site into the bile duct during T-tube limb removal. This may be caused by severe adhesions of the tube as well as suturing of the T-tube to the duct channel (7). Sharma and Farah (8) reported nine cases of T-tube fragment retained in the common bile duct. They were removed immediately in four cases (two cases with ERCP, one case with percutaneous radiological approach, one case with surgery), since the T-tube was known to have been fractured during removal. However, the other five cases remained asymptomatic for 2-36 years until cholangitis appeared (8).

For cases where the T-tube fragment remains asymptomatic for a certain period, patients may have unexplained abdominal pain, jaundice, cholestasis, and related symptoms. T-tube fragments retained in the common bile duct lumen should be taken out immediately the diagnosis is made. Radiological, surgical, and endoscopic procedures are alternatives to removing such fragments. However, ERCP should be the initial procedure in the management, if possible. Surgical procedures should be scheduled only if radiological or endoscopic interventions fail (9).

Although primary closure of the common bile duct is safer and more effective than T-tube drainage, there is still a wide use of T-tube after choledochotomy among surgeons. Choleperitonitis is one of the most severe complications resulting from leakage of bile from the choledochotomy site due to insufficient fistula formation after removal (10). In our opinion, these complications are more frequent than mentioned among surgeons, since most of them are not reported.

Other rare complications caused by T-tube breakage during removal occur mainly due to the improper suturing of the duct to the channel or inflammatory reactions to the drainage material. Thus, the tube fragment remains in the common bile duct lumen. In this case, the presentation is quite variable depending on the clinical status of the patient and texture of the drain. Although patients may remain asymptomatic for years, bile duct stones, cholangitis, and even common bile duct injury can be seen early or late after the breakage. Measures that could be taken to reduce the risk of T-tube breakage during removal include careful T-tube preparation, prevention of partial separation, use of latex drains, preventing T-tubes from being accidentally erected in the channel of the wall, and preventing prolonged placement (11).

Retention of T-tube fragments upon removal requires immediate surgery to avoid potential serious complications. ERCP should be the initial step to remove such fragments in centers where it is available. Otherwise, surgical approach will be mandatory, but re-exploration of the biliary tract increases surgical complications, especially bile fistula and stricture formation (12).

CONCLUSION

Broken T-tube fragments should be removed immediately to avoid potentially fatal complications due to the breaking of the T-tube fragments. The first step to avoid reoperation is to intervene endoscopically.

Informed Consent: Informed consent was obtained from the patient after providing detailed information about the surgery.

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A Rare Presentation of Retinoblastoma as a Fungating Orbital Mass: A Case Report

Kenan Kıbıcı[1], Berrin Erok[2], Onat Akın[3]

[1]Altınbaş University, Bahçelievler Medical Park Hospital, Clinic of Neurosurgery, İstanbul, Turkey
[2]Cihanbeyli State Hospital, Clinic of Radiology, Konya, Turkey
[3]Patomed Laboratory, Department of Pathology, İstanbul, Turkey

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ABSTRACT

Retinoblastoma (RBL) arises from the precursor cells of the retinal neuroepithelium. It is the most common primary malignant intraocular tumor in children. Primary orbital RBL is an extraocular disease detected clinically or radiologically at the time of diagnosis. It is a direct metastasis of an intraocular RBL. It very rarely presents as an exuberant fungating orbital mass, like in the present case, and is found in more advanced, untreated cases. Magnetic resonance imaging (MRI) is the preferred imaging modality for the evaluation of the tumor, vital orbital structures such as the optic nerve, and intracranial involvements. Computed tomography (CT) is useful in the evaluation of adjacent bony structures and calcifications. Herein, we report the case of a 3-year-old boy who presented to our clinic with a large, rapidly growing cauliflower-like mass protruding out of the left orbit and invading the surrounding soft tissues. MRI showed a10×8×7.5 cm^3 infiltrative heterogeneously enhancing left orbital mass with some necrotic and hemorrhagic components. Metastatic leptomeningeal enhancements were widespread in the intracranial region. CT revealed erosive destructive changes at the lateral orbital wall. Following left orbital enucleation, the diagnosis of RBL was made by histopathological examination, which showed sporadic Flexner-Wintersteiner type rosette formations. The patient underwent surgery and thereafter received radiotherapy and adjuvant chemotherapy. No recurrence was observed after 5 years. Although rare, orbital extension of RBL is one of the major contributors to mortality. Early diagnosis and detailed radiological evaluation are necessary to establish intracranial involvement and distant metastasis at the time of diagnosis.

Keywords: Primary orbital retinoblastoma, Flexner-Wintersteiner rosette, magnetic resonance imaging (MRI), leptomeningeal metastasis

INTRODUCION

Various neoplasms can arise from orbital structures. Retinoblastoma (RBL) is a neoplasm that arises from the retina, affecting the precursor cells of the retinal neuroepithelium. It is the most common primary malignant intraocular tumor in children. It is exclusively found in young children, and most cases were diagnosed before the age of five (1). RBL may be sporadic or secondary to a germline mutation associated with the inactivation of the RBL protein tumor suppressor gene, which is usually inherited. The hereditary form, which constitutes approximately half of the cases, tends to occur bilaterally at younger age (2,3). Affected children are also at increased risk of developing trilateral RBL (unilateral orbital RBL and pineoblastoma) and osteosarcoma (4). Sporadic disease forms usually occur in older children and are typically solitary (1). Primary orbital RBL is diagnosed as an extraocular disease and a direct extension of intraocular RBL. It is

ORCID IDs of the authors: K.K. 0000-0002-5912-9648; B.E. 0000-0001-8036-547X; O.A. 0000-0002-9878-8726.

Corresponding Author: Berrin Erok,
E-mail: drberrinerok@hotmail.com

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very rarely reported in developed countries due to early diagnosis and treatment. However, in developing and underdeveloped countries, extraocular extension of RBL is not an unusual presentation and is one of the major factors of poor prognosis. It is different from secondary orbital RBL, which is defined as orbital recurrence several weeks to years after enucleation for intraocular RBL. The most frequent manifestations are leukocoria (a white pupil), similar to that in intraocular RBL or proptosis (5). In more advanced and untreated cases, massive extraocular tumor spread very rarely results in a fungating giant orbital mass, as in the present case. Diagnosis is made by histopathological examination. In patients with extraocular extension of RBL, radiological imaging is important to determine the exact size and extent of the tumor. Herein, we report a case of a primary orbital RBL with intracranial involvement at the time of diagnosis in a 3-year-old boy.

CASE PRESENTATION

In August 2013, an otherwise healthy 3-year-old boy presented to our clinic with a giant, rapidly enlarging cauliflower-like mass protruding out of the left orbit and invading the surrounding soft tissues (Figure 1). He recalled that the lesion appeared approximately 6 months earlier and started to grow rapidly for the last 3 months. On physical examination, no regional lymph node enlargement or organomegaly was detected. Magnetic resonance imaging (MRI) of the orbit showed a 10x8x7.5 cm^3 solid infiltrative left orbital lesion obliterating the superior orbital fissure. The globe and retro-orbital structures lost their normal morphology. The left optic nerve (ON) was indistinguishable (Figure 2). There were some areas of necrosis on T2-weighted images (T2-WI) (Figure 2) and some linear hemorrhagic components on T1-WI (Figure 3). The mass extended into the left ON through the orbital apex into the optic chiasm, which was occupied by a nodular component of the mass (Figure 4). Following contrast administration, non-necrotic areas of the mass showed moderate to marked enhancement (Figure 5). In the intracranial region, enhanced metastatic meningeal lesions

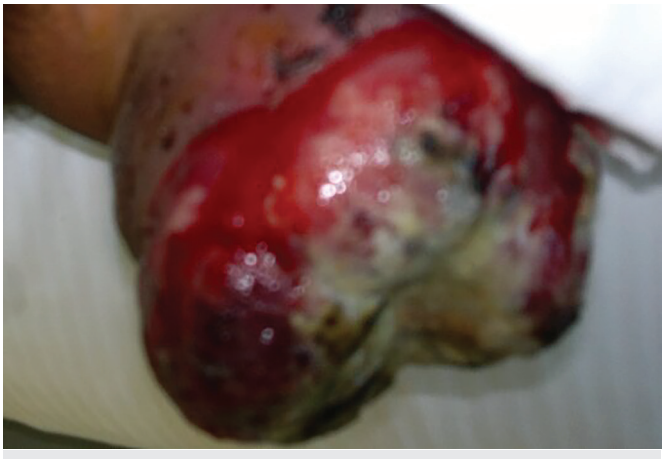

Figure 1. A large, cauliflower-like mass protruding out of the left orbit and invading the surrounding soft tissues in a 3-year-old boy

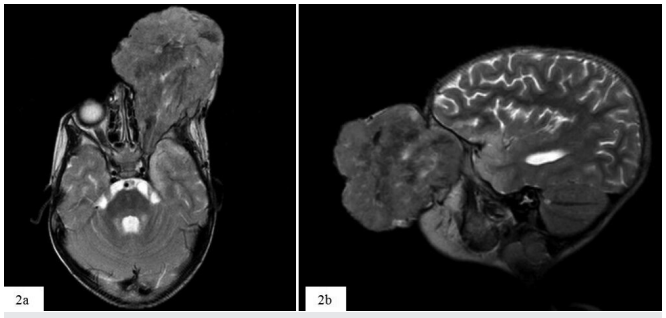

Figure 2. (a) Axial and (b) sagittal T2-weighted magnetic resonance images of the left orbit showing exophytic left orbital mass, which is heterogeneously isointense to the cortical gray matter with some areas of necrosis. The superior orbital fissure is obliterated, and the left optic nerve is indistinguishable

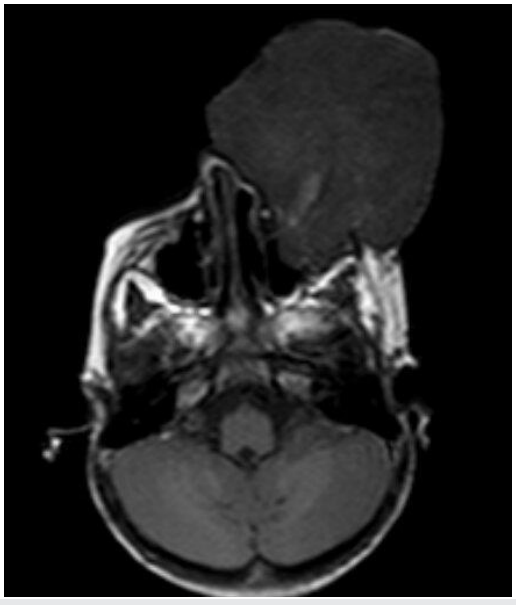

Figure 3. Axial T1-weighted magnetic resonance image showing some linear hyperintense hemorrhagic components

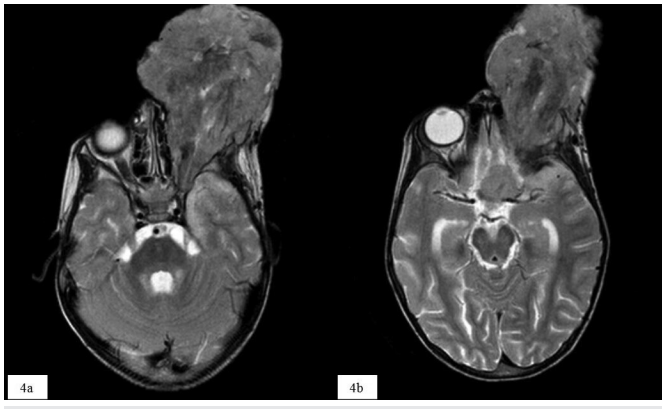

Figure 4. Axial T2-weighted magnetic resonance image showing (a) the extension of the mass into the left optic nerve through the orbital apex into the optic chiasm and (b) a nodular component of the mass occupying the optic chiasm

J Acad Res Med 2020;10(3):298-302

were detected in both supratentorial and infratentorial regions. The lesions were the widest at the left middle cranial fossa on the temporal lobe (Figure 6). On computed tomography (CT), the lesion was isodense compared with the vitreous, and there were erosive destructive changes at the lateral orbital wall, with no extension into the maxillary and ethmoid sinuses. There were some hemorrhagic foci, but no calcification was detected (Figure 7). Further systemic evaluation revealed neither systemic metastasis nor adrenal mass or paravertebral lesion suggesting orbital metastasis of neuroblastoma (NBL). Primary orbital NBL, primary orbital RBL, and orbital rhabdomyosarcoma (RMS) were considered in the differential diagnosis. Following left orbital enucleation, the diagnosis of orbital RBL was made by histopathological examination, which showed orderly proliferation of neoplastic cells with trabecular and insular pattern, occasionally presenting as Flexner-Wintersteiner type rosette formation (Figure 8). After surgery, the patient received radiotherapy and adjuvant chemotherapy. The patient was seen again in 2018, but no recurrence was observed.

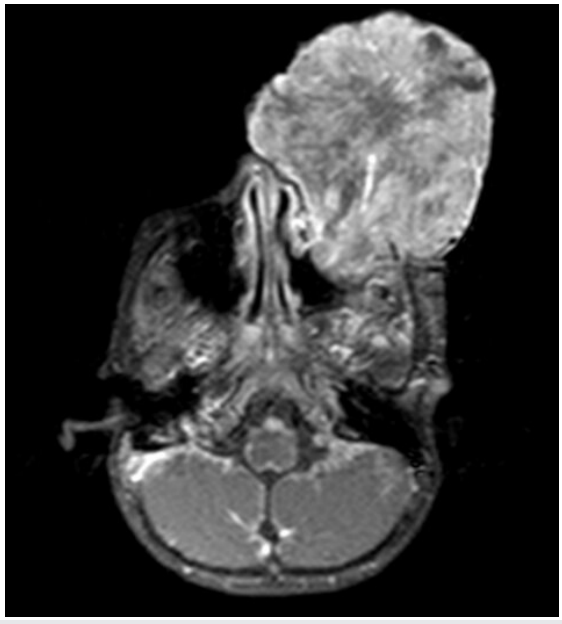

Figure 5. Axial T1-weighted fat-saturated magnetic resonance image with gadolinium showing moderate to marked enhancement in non-necrotic areas of the mass

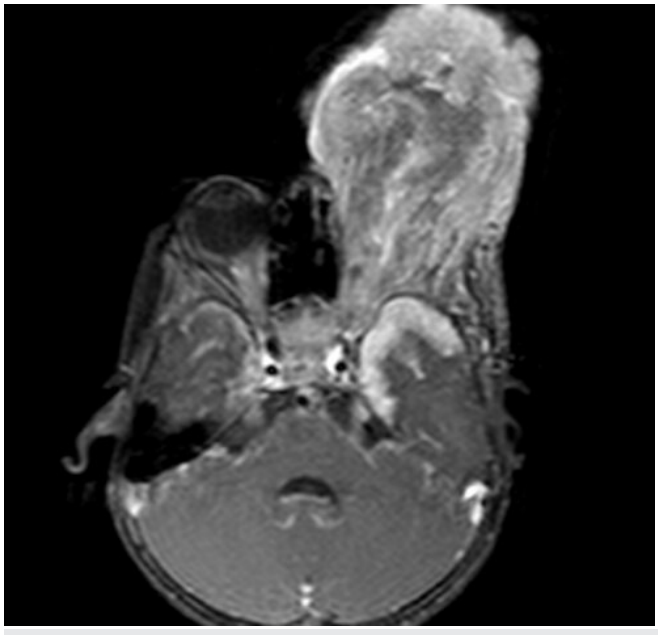

Figure 6. Axial T1-weighted fat-saturated magnetic resonance image with gadolinium showing metastatic leptomeningeal enhancement at the left temporal pole

Informed consent has been taken from the family of our patient.

DISCUSSION

Primary orbital RBL is defined as an orbital extension of an intraocular RBL detected clinically or radiologically at the time of diagnosis (1). The term, microscopic orbital RBL, is used when an enucleated eye with intraocular RBL demonstrates ON invasion, evident scleral infiltration, or extrascleral extension on histopathological evaluation (6). Clinical presentation with an exuberant fungating orbital mass, as in the present case, is very rare and found in more advanced, untreated cases due to

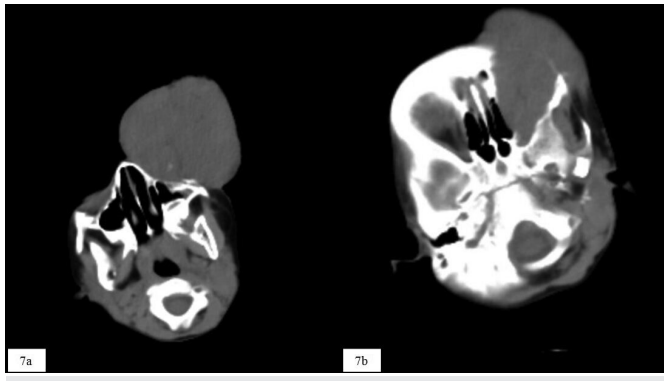

Figure 7. Axial computed tomography scan showing (a) the left orbital mass with some hemorrhagic foci but no calcification and (b) erosive destructive changes at the lateral orbital wall

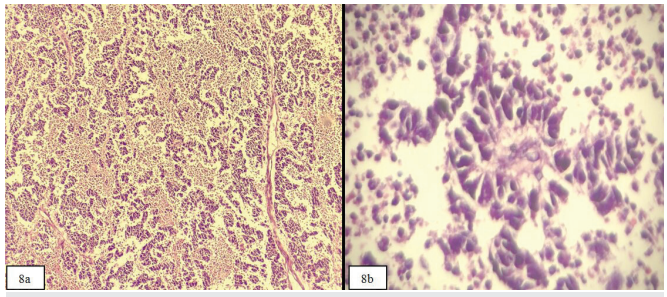

Figure 8. Histopathological examination showing (a) orderly proliferation of neoplastic cells with trabecular and insular patterns, occasionally forming rosettes (hematoxylin-eosin, x40). (b) Sections show a close-up view of a Flexner-Wintersteiner type rosette formation (hematoxylin-eosin, x400)

J Acad Res Med 2020;10(3):298-302

massive extraocular tumor spread through the ON or sclera. Both MRI and CT are used to assess the exact size and extent of the tumor. MRI, with its excellent soft tissue contrast, is the preferred imaging modality for the orbits and brain and for the evaluation of the tumor, vital orbital structures like the ON, and intracranial involvements. In addition, MRI enables diffusion-weighted imaging (DWI) that is valuable in monitoring treatment response. CT is useful in the evaluation of adjacent bony structures and calcifications. Following contrast administration, moderate to marked enhancement is seen in non-necrotic parts of the tumor. The rapid growth of the tumor results in necrosis and heterogeneous enhancement. On DWI, the enhancing viable part of the tumor tissue shows restricted diffusion associated with apparent diffusion coefficients lower than those of non-viable necrotic tissues. However, since these imaging features are not specific for RBL, histopathological examination is needed for exact diagnosis. In the present case, the differential diagnosis included embryonal RMS, primary orbital NBL, and primary orbital RBL, all of which share similar histology that basically consists of small round blue cells. RMS is the most common primary orbital malignancy in children (7). Clinical presentation is a typical rapidly growing mass, often in the upper inner quadrant of the orbit (8). On histopathological examination, embryonal RMS, which accounts for the majority of orbital RMS cases, is differentiated by the presence of rhabdomyoblasts. By contrast, NBL is the most common metastatic orbital tumor in children, with the primary focus in the adrenal medulla or paravertebral sympathetic/parasympathetic tissue of the abdomen and chest. In our patient, CT of the chest and abdomen did not reveal remarkable findings. Very rarely, NBL may be found as a primary orbital NBL without any systemic disease (9). Histologically, the undifferentiated part of the RBL demonstrates small blue cells with large hyperchromatic nuclei and scant cytoplasm. Homer Wright Pseudorosettes and Flexner-Wintersteiner Rosettes may be seen. Homer Wright Rosettes are differentiated tumor cells grouped around a central region containing neuropil and are therefore associated with tumors of neuronal origin and found in other tumors like pancreatic neuroendocrine tumors. On the contrary, Flexner-Wintersteiner Rosette is a relatively unique characteristic of RBL. In our patient, occasional Flexner-Wintersteiner type rosette formation was found and the tumor was differentiated from NBL. Since the orbital extension of the intraocular RBL increases the risk for regional and systemic dissemination of the disease compared with patients without extraocular disease, detailed evaluation is mandatory (10). The most common metastatic dissemination of RBL occurs intracranially via the ON in which the subarachnoid space of the ON sheath is infiltrated by the tumor cells with dissemination into the cerebrospinal fluid (5). Therefore, MRI of the brain and spinal cord should be performed at the same time to assess leptomeningeal metastases in patients with extraocular extension of RBL. Brain MRI is also necessary to rule out trilateral RBL. In the present case, both supratentorial and infratentorial leptomeningeal metastases were found on the brain MRI at the time of presentation. In RBL, lymphatic spread to regional lymph nodes depends on the involvement of the conjunctiva or eyelids due to the absence of lymphatics in most of the globe and the orbit. Preauricular lymph nodes are most commonly affected in these patients (1). Therefore, they should be carefully palpated in clinical examination, and fine-needle aspiration biopsy should be done in case of suspicion. Metastasis to the lungs, bone, bone marrow, and liver may occur hematogenously. Skeletal metastases are best evaluated by bone scintigraphy or fluorodeoxyglucose positron emission tomography, because the highly hematopoietic bone marrow in infants makes it difficult to detect bone marrow involvement on MRI. On post-treatment follow-up, MRI is the preferred modality for the assessment of treatment response and detection of local and distant recurrences because of the increased long-term risk for malignancy in young patients who undergo repetitive CT. Currently, there are no standard treatment protocols for orbital RBL. Good long-term survival results have been reported with multimodal treatment, including high-dose chemotherapy, orbital enucleation, radiotherapy, and additional adjuvant chemotherapy over the last years. However, extraocular extension of RBL is still a major contributor to mortality, and patients have a poor prognosis (5).

CONCLUSION

Despite its rare occurrence in developed countries due to early diagnosis and treatment, primary orbital RBL is one of the major contributors to mortality. Early diagnosis and detailed radiological evaluation are essential to establish intracranial involvement and distant metastasis at the time of diagnosis. MRI, with its high tissue contrast and improved spatial resolution, is the mainstay in the diagnosis and follow-up of patients. Survival can be increased with early multimodal treatment and close radiological follow-up.

Informed Consent: Informed consent has been taken from the family of our patient.

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Conflict of Interest: There is no any conflict of interest among the authers.

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Giant Juvenile Fibroadenoma of the Breast: Clinical Manifestation in Two Cases

Mehmet Tolga Kafadar[1], Mehmet Ali Kırşan[1], Suat Çal[2], Mehmet Hanifi Okur[2], Sadullah Girgin[1]

[1]Dicle University Faculty of Medicine, Department of General Surgery, Diyarbakır, Turkey
[2]Dicle University Faculty of Medicine, Department of Pediatric Surgery, Diyarbakır, Turkey

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ABSTRACT

Giant fibroadenomas are benign masses that usually present as unilateral rapid growths in the breast during puberty. They can spread over a wide area and cause congestion and ulcerations in the breast skin. Definitive diagnosis is made by breast biopsy. Treatment options may vary from simple excision to subcutaneous mastectomy, depending on the size of the mass. Herein, we present two cases of 13- and 14-year-old female patients who were treated for giant breast fibroadenoma. In these extremely rare cases, total mass excision was performed, which preserved the breast skin.

Keywords: Breast, juvenile giant fibroadenoma, surgery

INTRODUCTION

Fibroadenomas are the most common causes of breast lumps in young women. They have a benign character and contain mixed glandular and mesenchymal structures. They are caused by increased estrogen stimulation and receptor sensitivity during puberty (1). They usually stop growing if they reach a size of 2 cm. Those over 5 cm in size are defined as giant fibroadenoma. Indeed, providing the best treatment for these patients in terms of clinical and psychological care is challenging. Attentive surgical planning is required to ensure a fine balance between adequate resection and the best cosmetic outcome for a developing breast (2). Herein, two different cases of a giant juvenile fibroadenoma of the left breast were presented.

CASE PRESENTATIONS

Case 1

A 13-year-old female patient was admitted to a general surgery outpatient clinic with a rapidly growing, painless mass in her left breast that she have noticed approximately 3 months ago. Physical examination revealed a firm, well-circumscribed, approximately 11 cm mass that filled the left breast (Figure 1a). No pathology was found in the right breast and in both axillae. Patient's family history and laboratory tests were unremarkable. Breast ultrasonography (USG) showed a 105x80 mm^2, well-circumscribed hypoechoic solid lesion that nearly filled the left breast (Breast Imaging-Reporting and Data System 4A).

ORCID IDs of the authors: M.T.K. 0000-0002-9178-7873; M.A.K. 0000-0003-0015-4870; S.Ç. 0000-0003-1964-0895; M.H.O. 0000-0002-6720-1515; S.G. 0000-0002-4889-7473

Corresponding Author: Mehmet Tolga Kafadar,
E-mail: drtolgakafadar@hotmail.com

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Case 2

A 14-year-old female patient was admitted to the general surgery outpatient clinic with a rapidly growing, painless mass in her left breast that she have noticed approximately 3 months ago. During physical examination, a firm, well-circumscribed mass of approximately 9 cm, which nearly filled the left breast, was palpated. The patient's medical and family histories were unremarkable. Breast magnetic resonance imaging (MRI) showed a lesion that nearly filled the left breast, with heterogeneous hypointense appearance on T2A images with a size of 82x78 mm, heterogeneous hyperintense characteristic in T1A images, marked heterogeneous enhancement after intravenous administration of contrast material in the upper inner quadrant, and slight diffusion restriction in the diffusion-weighted images (Figure 1b).

Tru-cut biopsy was performed on the left breast in both cases. The results revealed fibroadenoma, and the patients underwent surgery. The masses were totally excised under general anesthesia, preserving the breast skin (Figure 1c). The resulting deformity was filled with the patients' own breast tissue (Figure 1d). Postoperative histopathological examination of the masses were interpreted as giant juvenile fibroadenoma (Figure 2). No recurrence was noted during the 3-month follow-up period.

DISCUSSION

Fibroadenomas are one of the most common causes of breast masses in adolescents and young women. Juvenile giant fibroadenomas account for 0.5% of all fibroadenomas. They are mostly solitary in nature, but multiple masses can be found in 10%-20% of the patients. They are usually unilateral and rarely seen bilaterally (3). The incidence increases in the second and third decades of life, and masses typically stop growing when they reach

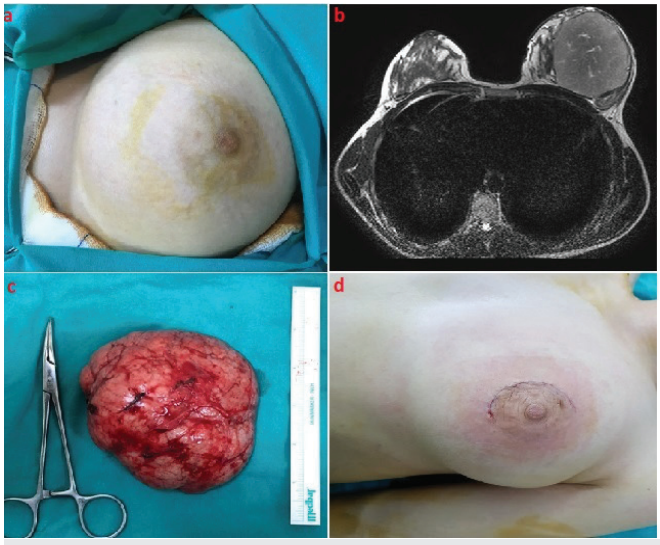

Figure 1. Preoperative view of the patient **(a)**, preoperative MRI of the patient **(b)**, macroscopic view of the excised specimen **(c)**, and postoperative incision view of the patient **(d)**
MRI: magnetic resonance imaging

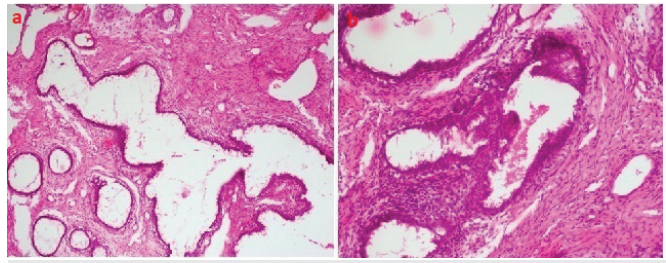

Figure 2. Microscopic view of the specimen; the tumor shows pericanalicular pattern growth, uniformly increased stromal cellularity, and epithelial proliferation without atypia (a,b) (hematoxylin and eosin staining, x100)

a size of 2-3 cm. They are generally benign, well-circumscribed, and encapsulated. Typically, large lesions grow rapidly. In rare cases, they can grow up to 15 cm in size. Very few fibroadenomas have irregular edges and may contain calcifications. The lesion may cause breast deformity, compression of surrounding tissues, nipple collapse, congestion, and skin ulcerations (4). Islam et al. (5) reported the world's largest juvenile fibroadenoma of the breast in a 16-year-old girl who presented with a 28x25 cm^2 mass on her left breast, which was treated conservatively. In the presented cases, the masses were unilateral, rapidly growing, well-circumscribed, and solitary, consistent with the literature.

Giant fibroadenoma, phyllodes tumor, juvenile macromastia, breast abscess, lipoma, hamartoma, and malignancies can be included in the differential diagnosis of large breast masses (6). Phyllodes tumors of the breast should be ruled out in the differential diagnosis. These tumors rarely occur during puberty, and they are often seen in the third to fourth decades of life. They do not have true capsules but have high cellularity and a tendency to metastasize (7).

Preoperative histopathological diagnosis is important for differentiating breast mass from phyllodes and malignant tumors. USG is usually sufficient for the diagnosis of giant fibroadenomas, but in some cases, MRI can be performed. MRI is generally indicated for atypical lesions. Mammography is not recommended in young patients (8).

Surgical planning should be made according to the localization and size of the mass. Small tumors can be easily removed through an areolar incision. Breast-conserving surgery and reconstruction with prosthesis can be performed in patients with small tumors. The excision of fibroadenomas can be performed under local or general anesthesia. Circumareolar or inframammarian incision is a good choice to minimize scar, but the location and size of the mass influence the selection of appropiriate incision. For masses located far from the areola border, a half-moon incision can be made directly over the mass. The mass should be totally excised (9). Skin excision and reduction may be required due to structural deformities after giant tumor excisions. Reductions made to ensure symmetry should be done after puberty, that is, after breast development (10). Skin excision was not performed

J Acad Res Med 2020;10(3):303-5

in our cases. A good cosmetic result was obtained by filling the deformity following mass excision with the patient's own breast tissue.

CONCLUSION

Juvenile giant fibroadenomas are rare tumors. They can grow rapidly and form deformities in the breast. USG and, if necessary, MRI are required for diagnosis. Definitive diagnosis is made by histopathological examination. Once diagnosed, good cosmetic results can be obtained with immediate and appropriate surgical treatment.

Informed Consent: Informed consent was obtained from the father of the patients presented in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - M.T.K., M.H.O.; Concept - M.T.K., M.A.K., S.Ç., S.G.; Design - M.T.K., S.Ç.; Data Collection and/or Processing - M.T.K., M.A.K., S.Ç., M.H.O.; Analysis and/or Interpretation - M.T.K., M.A.K., S.G.; Literature Search - M.T.K., M.H.O., S.G.; Writing Manuscript - M.T.K.

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Anesthetic Approach for a Patient with 1q21.1 Microdeletion Syndrome: A Case Report

Gül Cansever, Cansu Uzuntürk, Nur Canbolat

İstanbul University, İstanbul Faculty of Medicine, Department of Anesthesiology and Reanimation, İstanbul, Turkey

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ABSTRACT

1q21.1 microdeletion syndrome is a chromosome abnormality where segment of genetic material on the long (q) arm of chromosome 1 at position 21.1 is missing or deleted. Distal 1q21.1 microdeletion is associated with microcephaly, macrocephaly, mental retardation, craniofacial dysmorphism, cardiac abnormalities, and cataracts, while proximal 1q21.1 microdeletion is associated with thrombocytopenia-absent radius syndrome and skeletal, cardiac, and genitourinary system abnormalities. Moreover, patients with 1q21.1 microdeletion syndrome have no unique facial features; however, 75% of the carriers have craniofacial dysmorphism. Short stature (50%), microcephaly (22%), cleft palate, cleft lip, long philtrum, frontal bossing, epicanthal folds, and bulbous nose can be seen among these patients. Although there is delay in motor development in 50%-75% of these patients, mental retardation is typically mild to moderate. Neurological symptoms such as tremor (44%), hyperreflexia (35%), and hypotonia (35%) have been reported in the literature. In addition, seizure occurs at a frequency of 10%-20% and starts at an early age. Psychiatric conditions such as autism spectrum, attention-deficit hyperactivity, and mood and anxiety disorders might also occasionally accompany 1q21.1 microdeletion syndrome. In this case report, we discuss our anesthetic experience with a 3-year-old boy diagnosed with this syndrome, for whom an orthopedic clinic planned a posterior spinal instrumentation. Further, this is the first case in the literature on anesthetic treatment of patient with 1q21.1 microdeletion syndrome.

Keywords: 1q21.1 microdeletion syndrome, difficult intubation, general anesthesia, posterior spinal instrumentation

INTRODUCTION

1q21.1 microdeletion syndrome is a rare disease. While some carriers of this microdeletion show no phenotype, some have craniofacial dysmorphism and cardiac, genitourinary, and neurological abnormalities (1-3).

CASE PRESENTATION

The orthopedic clinic planned a posterior spinal instrumentation for a 3-year-old, 12 kg male patient diagnosed with 1q21.1 microdeletion syndrome. Additionally, parental's informed consent was obtained.

The patient was born in the 27th gestational week by emergency cesarean delivery due to fetal bradycardia. Moreover, he was intubated and taken to the newborn intensive care unit (ICU) due to lack of spontaneous breathing. Later on, ultrasonography revealed hemorrhage in the left periventricular region leading to a moderate communicating hydrocephalus. Echocardiography showed patent foramen ovale and mild mitral insufficiency. Later, cerebral palsy and premature retinopathy were diagnosed.

ORCID IDs of the authors: G.C. 0000-0001-9627-2294; C.U. 0000-0001-8266-8888; N.C. 0000-0003-1490-3027.

Corresponding Author: Nur Canbolat,
E-mail: drnurekiz@gmail.com

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Genetic analysis conducted during ICU hospitalization revealed 1q21.1 microdeletion in his mother and himself.

In preoperative anesthesia examination, he had scaphocephaly, long philtrum, and pointed forehead (Figure 1). Difficult airways were predicted since the patient's Mallampati score was 3. Physical examination demonstrated weakness in the right arm and imbalanced walking when taking the right step. Mild mitral insufficiency persisted in the latest echocardiography performed by the pediatric cardiologist; thus, postoperative heart rate, blood pressure, electrocardiography, and electrolyte follow-up were recommended.

Various sizes of face masks, endotracheal tube (ETT), Miller and Macintosh blade, stylet, and laryngeal mask airway were prepared for intubation. Moreover, peripheral oxygen saturation, electrocardiography, non-invasive blood pressure, and core temperature monitoring were installed. Anesthesia induction was also performed with 8% sevoflurane. The mask ventilation with airway was done by two anesthetists. Further, the patient received fentanyl 1 mcg/kg and rocuronium 0.6 mg/kg intravenously. He had a Cormack-Lehane score of 1 and was easily intubated with a 4.0-cuffed ETT on Macintosh 1 blade. Volume-controlled ventilation began with a positive end-expiratory pressure of 4 cm H_2O and median peak pressure of 19 cm H_2O, enabling tidal volume of 6-8 mL/kg. Also, invasive arterial pressure monitoring was performed, and central venous catheter was then inserted. Additionally, anesthesia was preserved with oxygen/air and remifentanil and propofol infusions. The patient was then given a prone position. When the peak pressure was elevated (above 30 cm H_2O) and $ETCO_2$ was low, pressure-controlled ventilation was initiated to prevent lung damage caused by the ventilator. He was also administered with methylprednisolone 12 mg intravenously and inhaler bronchodilators to prevent airway edema. Tidal volume was reduced to less than 6 mL/kg; thus, peak pressure returned to normal (16 cm H_2O). Somatosensory and motor evoked potentials were also monitored. The estimated blood loss (130 mL) was supplemented by 750 mL of crystalloid solution, and the urine output was 33 cc. The surgery lasted for 200 minutes. Moreover, postoperative analgesia was achieved with 15 mg/kg paracetamol and 1 mg/kg tramadol. The supine position was then restored, and after extubation, he was transported to the ICU. Erythrocyte suspensions of 25 mL/kg (~300 mL) and fresh frozen plasmas of 15 mL/kg were also administered. After 5 days, he was discharged.

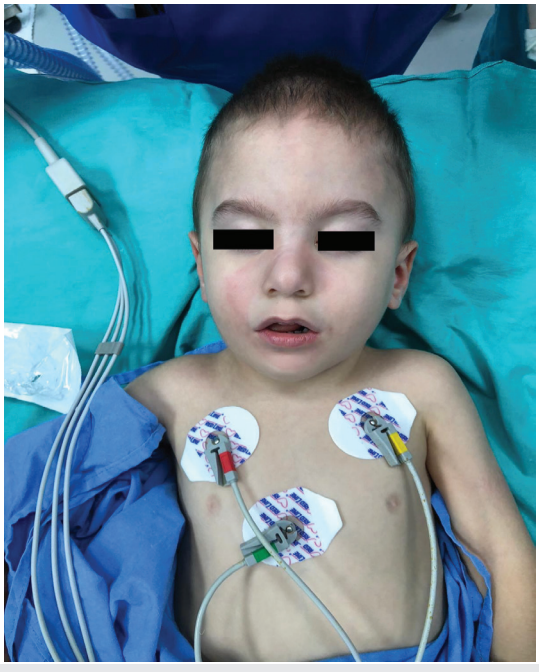

Figure 1. Frontal view and facial anomalies of the patient

DISCUSSION

1q21.1 microdeletion syndrome is clinically characterized by variable phenotypes. Craniofacial dysmorphism is one of the causes of difficult airways (4). If suspected, difficult intubation equipment and ancillary health personnel should be present in the operating room.

Cardiac evaluation of the patient is important in terms of mitral valve and congenital heart diseases and atrial fibrillation (1,5). Our patient's patent foramen ovale closed with medical treatment and mild mitral insufficiency persisted.

Increased secretion caused by crying and his prone position contributed to an increase in peak pressure. Barotrauma was avoided through aspiration, switching to pressure-controlled ventilation and targeting the lowest peak pressure.

Special attention should be paid to thrombocytopenia when dealing with 1q21.1 microdeletion (3).

Neurology consultation should be needed. The potential interaction of the patient's own medications and the drugs used in anesthesia is significant in reducing perioperative morbidity and mortality. His physical examination revealed loss of strength in his right arm and an imbalance due to cerebral palsy.

CONCLUSION

1q21.1 microdeletion is a rare syndrome concerning many systems and should be further studied. This syndrome requires a thorough preoperative anesthesia examination and preparation for possible complications in the operating room. Since this condition is associated with craniofacial dysmorphisms, difficult airways should be considered. Although respiratory distress was not an established characteristic of 1q21.1 microdeletion, it was experienced in our case. Furthermore, we treated bronchospasm with inhaler bronchodilators, intravenous steroids, and ventilator-induced lung injury prevention strategies such as low tidal volume and peak pressure.

Informed Consent: Parental's informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - G.C.; Concept - G.C.; Design - G.C.; Data Collection or Processing - G.C.; Analysis and/or Interpretation - N.C.; Literature Search - C.U., N.C.; Writing Manuscript - C.U., N.C.

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2020 REFEREE INDEX

A. Başar Tekin
Abdülhamit Mısır
Abdullah Çırakoğlu
Adnan Taş
Ahmet Serkan İlgün
Ali Ayyıldız
Ali Çift
Ali Yavuz Karahan
Altay Sencer
Aslı Şahin Yılmaz
Aydın Aydoseli
Aylin Özdilek
Ayşe Çiğdem Tütüncü
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Onur Tutar
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Volkan Kara
Volkan Selmi
Volkan Öter
Yaprak Ataker
Yetkin Zeki Yılmaz
Zafer Çiftci
Zahra Polat
Zeliha Matur

2020 AUTHOR INDEX

2020 AUTHOR INDEX

2020 SUBJECT INDEX

2020 SUBJECT INDEX

2020 SUBJECT INDEX

2020 SUBJECT INDEX