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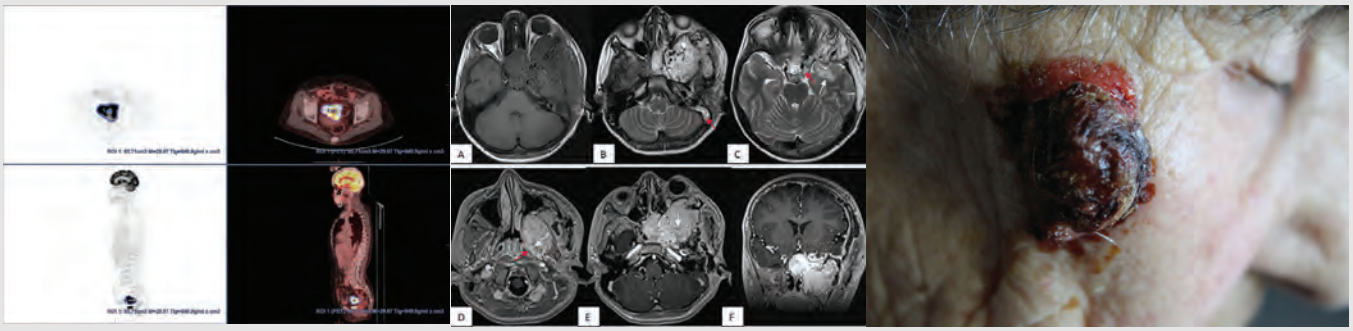

Highlights

galenos yayınevi

Official Journal of University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital

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Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

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Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

European Archives of Medical Research

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Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

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Case Series: The Case Series section reports a series of 2-6 similar cases. The cases should address a challenging diagnostic and/or therapeutic problem with possible solutions to help clinicians in managing these cases. Case series must be accompanied with a comprehensive review of literature. It should include six authors maximum. Structure of manuscript should include Introduction, Case Series, Discussion, Conclusion. It should have 3-5 keywords maximum. Please check Table 1 for the entire limitations for Case Series.

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Image(s): The number of images is left to the discretion of the author. (See Original article section)

Figure Legend: Reference citations should appear in the legends, not in the abstract. Since there is no manuscript text, the legends for illustrations should be prepared in considerable detail but should be no more than 500 words total. The case should be presented and discussed in the Figure legend section.

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables.

Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text).

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Original Article	3500	250 (Structured)	40	6	7 or total of 15 images
Review Article	5000	250	80	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

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Journal Article: Stephane A. Management of Congenital Cholesteatoma with Otoendoscopic Surgery: Case Report. Turkiye Klinikleri J Med Sci 2010;30:803-7.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press;2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme;2003.

Conference Proceedings: 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. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dçent Res. 1974. Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 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

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COVID-19 Vaccines

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Abstract

The World Health Organization declared coronavirus disease-2019 (COVID-19) as a "Public Health Emergency" of international importance on January 30, 2020, and as a "Pandemic" on March 11, 2020. In the fight against coronavirus, the most important strategy in protection from the disease is the "Vaccine", due to the fact that the coronavirus is very contagious, the complications and death it causes. In this review, there is information about current vaccines, their effectiveness and studies that play a role in protection against COVID-19.

Keywords: COVID-19, vaccine, efficacy

INTRODUCTION

Inactivated Vaccines

Inactivated vaccine production is a more traditional method. Many inactivated vaccines have been developed for various viruses, such as influenza, hepatitis A, and poliovirus (1). Inactivated vaccines contain killed pathogens through physical or chemical processes; therefore, they cannot cause disease and are considered safe (2). Adjuvants are used to strengthen the immune response to vaccines (3), and their storage and transportation conditions are easier to achieve than in those of other vaccine types. They can be stored at 2 °C-8 °C. However, there are some disadvantages: i) Large amounts of virus or bacteria are needed to produce vaccines; ii) during the inactivation process, the immunogenicity of the pathogen can be affected; and iii) booster doses are generally needed to produce adequate immune response (2,4). Since the start of the coronavirus disease-2019 (COVID-19) pandemic, nine inactivated vaccines have been authorized for emergency use by many countries, so far, including CoronaVac developed by Sinovac Biotech (China), BBIBP-CorV by Sinopharm (China), and BBV152 (Covaxin) developed by Bharat Biotech (India) (5). Only two of them were approved by the World Health Organization (WHO), i.e., CoronaVac and BBIBP-CorV, as of August 2021 (6).

Phase III clinical trials of CoronaVac were conducted in China, Brazil, Turkey, Chile, Indonesia, Philippines, and Hong Kong (6), and some of them are still ongoing. The Brazilian trial demonstrated an efficacy of 51% [95% confidence interval (CI) 36-62] against symptomatic disease, whereas the Indonesian and Turkish trials presented 65% (95% CI 20-85) and 84% (95% CI 65-92), respectively. By contrast, the efficacy of vaccines against hospitalization was 100% in Turkey (95% CI 20-100) and Brazil (95% CI 56-100). In Chile, a cohort study of more than 10 million individuals was conducted. They were followed for 2 months after vaccination, and vaccine effectiveness was assessed. The efficacy rates against symptomatic COVID-19, hospitalization, intensive care unit admission, and death were 67% (95% CI 65-69), 85% (95% CI 83-97), 89% (95% CI 84-92), and 80% (95% CI 73-86), respectively (7-9). On June 1, 2021, the WHO validated the vaccine for emergency use, and 39 countries including Turkey were granted emergency use of authorized vaccines as of August 12, 2021. The efficacy of BBIBP-CorV (Sinopharm) was evaluated in the COVIV-02 study. It is being conducted in

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Bahrain, Egypt, United Arab Emirates, and Jordan (clinicaltrials.gov, NCT04510207). Interim results showed an efficacy of 78.1% (95% CI 64.8-86.3%) against non-severe COVID-19. The WHO approved BBIBP-CorV for use on May 7, 2021, and it is being used in 59 countries as of August 12, 2021 (7). BBV152 (Covaxin) vaccine demonstrated an efficacy of 77.8% (95% CI 65.2-86.4) against symptomatic disease and 93.4% (57.1-99.8) against severe disease in a phase 3 clinical trial in India (10). This vaccine has been approved in nine countries, including Guyana, India, Iran, Mauritius, Mexico, Nepal, Paraguay, Philippines, and Zimbabwe, as of August 2021.

Variants of concern: A study revealed that serum samples obtained from individuals who received two doses of CoronaVac showed nearly the same neutralization activity against alpha (B.1.1.7) variant but significantly reduced activity against beta (B1.351) and gamma (P.1) variants (11). In another study, Wang et al. (12) revealed similar results for BBIBP-CorV vaccine against alpha and beta variants.

A report evaluating the efficacy of BBV152 showed a decreased neutralization activity against beta, gamma, delta (B.1.617.2), and kappa (B.1.617.1) variants, whereas the activity was quite similar against the alpha variant. In the same study, vaccine effectiveness was 65.2% (95% CI 33.1-83.0) against the delta variant (10). Further studies are warranted to get a better understanding of the efficacy of inactivated vaccines against new variants.

Nucleic Acid Vaccines

Nucleic acid vaccines are DNA and mRNA vaccines. DNA vaccines enable the expression of target proteins in the individual who was vaccinated. These vaccines consist of plasmid DNA containing the gene of the target protein and mammalian expression promoter regions. Its routine usage has been avoided because of drawbacks, such as low immunogenicity, reliance on mRNA for function, and possibility of being mutagenic by interacting with the recipient DNA (13). Although mRNA vaccines were originally utilized during the COVID-19 pandemic, the first studies on these vaccinations were conducted in 1989. The ability of mRNA packaged in a cationic liposomal nanoparticle (LNP) to enter multiple eukaryotic cells was first demonstrated; subsequently, when naked (unprotected) mRNA was injected into mouse muscle cells, it remained stable for several days and generated target antigens (14). These findings show that using an *in vitro* transcription mRNA molecule rather than plasmid DNA to enable the production of a targeted protein in living tissue without the use of a viral carrier is safer (vector) (14,15). Because the mRNA molecule acts in the cytoplasm rather than in the nucleus, there is no risk of insertional mutagenesis when it joins the host genome, and its structure can be destroyed by normal cellular activity; thus, its half-life can be controlled by various chemical modifications (16).

One of the most significant advantages of the molecule is that it can be turned into a more effective molecule by modifying it chemically to make it more stable and translatable (17). It is not dependent on a viral vector for *in vivo* activity and does not induce side effects caused by antivector immunization as it allows rapid uptake and expression into the cytoplasm with carrier molecules (18,19). Self-amplifying and self-replicating vaccines and conventional (non-replicating) vaccines are two types of MRNA vaccines. RNA-dependent RNA polymerases are commonly used in self-replicating mRNA vaccines to promote mRNA amplification and target antigen expression. Long-term antigen production is guaranteed in this manner; however, the vaccine has a huge molecular structure because it comprises numerous promoter regions and necessitates transport by viral vector (20).

In contrast, traditional mRNA vaccines are synthetic molecules made *in vitro* from plasmid DNA and bacteriophage RNA polymerase (15,16) The created unprotected mRNA molecules must be packed with lipid nanoparticle carriers so that they can enter the target cells via endocytosis. LNPs also shield these compounds from enzymatic degradation (21,22). Furthermore, lipid nanoparticles enable the regulated distribution of mRNA molecules in the body, allowing them to reach their target cells (16).

To induce immunogenicity, mRNA vaccines must first reach the ribosomes and ensure the production of target antigens. After this target intracellular endogenous antigen is synthesized, it is presented to CD8+ T-cells by major histocompatibility complex (MHC) class I molecules, which sensitize them. Additionally, antigen-presenting cells use MHC class II molecules to activate CD4+ T lymphocytes. This is very important in the induction of humoral immunity as well as cellular immunity. In addition, antigen-presenting cells transport the antigens to the lymph nodes, where they are transferred to non-sensitive B-cells, triggering the immunological process that leads to antibody production. Memory B-cells are activated when a vulnerable individual is exposed to target antigens again. In conclusion, mRNA vaccines provide cellular and humoral immunity by activating CD4+, CD8+ T-cells, and B lymphocytes (23-25). According to the WHO, 184 vaccine candidates are in preclinical development and 112 are in clinical trials for COVID-19, with 11 and 18 being DNA and RNA vaccines, respectively (26). Of

these vaccines, Pfizer/BioNTech BNT162b2 has been licensed by the Food and Drug Administration (FDA) for use in individuals aged >16 years and has been approved for emergency use for individuals aged 12-16 years (27). Moderna's mRNA-1.273 vaccine also has been licensed for emergency use to prevent COVID-19 (28).

BNT162b1 and BNT162b2 mRNA vaccines were created by Pfizer/BioNTech. The severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) spike protein is encoded in both vaccines, which are packed with LNP and undergo nucleotide modification. In phase I/II trials, both vaccines were proven to be efficacious and safe in prime and boost vaccine regimens, and BNT162b2 was able to advance to phase II/III studies (NCT04368728) because it has milder adverse effects (29). In a phase III study including 43,000 patients aged ≥16 years, the case group received 30 µg of the vaccine, and the control group received the same quantity of saline solution at 3-week interval. Vaccine efficacy was measured 7 days after the second dose, with rates of 95% and 94.6% in those without and with a history of COVID-19, respectively. The findings of this investigation show that BNT162b2 is efficacious and safe against COVID-19 (30). The vaccine's efficacy against symptomatic disease declined with time, from 90% at the end of the second month to 84% at the end of the sixth month, according to an unpublished follow-up report that included phase III participants (31). Although the vaccine's neutralizing antibody levels were lower against beta and delta variants, investigations have indicated that it maintains neutralizing effectiveness against variants of concern (32,33). The BNT162b2 vaccination should be given in two intramuscular doses of 0.3 mL each at an interval of 3 weeks. The time between the two doses can be extended up to 42 days, but not less than 3 weeks. If the vaccine was not administered at this time, the schedule should be re-established (34,35). Because most studies involved two doses, the protective effectiveness and durability of a single dose are uncertain. Furthermore, a single-dose vaccine was found to be ineffective against the alpha, beta, and delta forms (36,37). In immunocompromised groups, such as recipients of chemotherapy, patients with hematological malignancies, recipients of hematopoietic stem cell and solid-organ transplantation, patients with human immunodeficiency virus (HIV), and others, a third dose has been advised, provided that it is given at least 28 days after the second dose (38). Local adverse effects such as redness, swelling, and pain at the injection site are common after the second dosage, whereas serious postvaccine reactions are rare. The majority of these reactions are mild and generally resolve within 2 days.

Fever, fatigue, headache, arthralgia, and myalgia are other symptoms that have been described (39). Anaphylaxis following vaccination was observed in five cases per million doses (40). Although Bell's palsy occurred during phase III clinical trials, no link between immunization and Bell's palsy was discovered (41). The surveillance system found no thrombosis-related events connected with mRNA vaccinations (42). Moderna's mRNA-1273 is another mRNA vaccination that has been licensed by the FDA for emergency use. The recommendation was to take two doses at 28 days apart. It contains the target antigen and spike protein lnp packed with the mRNA molecule (43).

Individuals aged 18-55, as well as those aged >55 years were studied in a phase I clinical trial. Despite the decline in CD8+ T-cell response, considerable CD4+ T-cell response was seen in both the groups, and they had comparable and sufficient effectiveness and safety profiles (44,45). In a phase III clinical trial, vaccination activity was shown to be 94.1% effective (14 days after the second dose) in avoiding symptomatic illness; however, adults aged >65 years accounted for 86.4% of this activity. This vaccine has also been studied with two doses, and the efficiency and safety of a single dosage are unknown (46). The side effects are comparable with those of BNT162b2 and are usually local reactions including pain, redness, and swelling at the injection site, which usually resolve within 2 days of vaccination. Fever, fatigue, headache, arthralgia, and myalgia are other symptoms that have been described. Although adverse effects are less likely to occur in individuals aged >65 years, they have been considered in this vaccine (47). Anaphylaxis was found in 2.8 cases per million doses after vaccination. A history of allergy was noted in 86% of these cases, and 90% of allergies occurred within half an hour after vaccination. In the United States, some cases of Bell's palsy are assumed to be related to the vaccine, but no link has been identified between vaccination and Bell's palsy because the rate is lower than the general population (48,49). In the United States, a case of postvaccine sinus vein thrombosis with thrombocytopenia was recorded; however, it was unclear if the link was accidental or causal and has been reported as an extremely rare side effect (49-51).

Viral Vector Vaccines

Although the traditional approach is being used when developing a vaccine to control the COVID-19 pandemic, viral vector vaccines have also been used based on molecular techniques. The basic characteristic of viral vector vaccines is that a genetic piece of the virus is transferred into another virus, and immunity is produced following administration of a vaccine to the body (52). In vaccines obtained through this method, an immune response resembling a real viral infection occurs (53). The characteristics of the carrier virus of a known structure

determine the side effects and production details of the vaccine. Thus, vaccine studies against a new and unknown pathogen can be conducted more securely. Replicable (attenuated) viruses and non-replicating (inactivated) viruses are used as carriers in these vaccines (53). Although vesicular stomatitis virus is most frequently used as a replicating carrier virus, adenoviruses are most often preferred as the non-replicating carrier virus (54). At present, carrier viruses are used in the vaccine production studies for Ebola, hepatitis C, influenza, tuberculosis, and HIV (55). By activating both cellular and humoral immunity, these vaccines produce long-term immunity. They are advantageous because they can be produced easily, can be applied to the mucosa, and are of low cost (56). In contrast, COVID-19 viral vector vaccines are based on the transfer of genes encoding the spike protein of SARS-CoV-2 via adenovirus. Although this technology was used in 17 vaccine candidates, only three adenoviral vector vaccines have been approved for use (57).

Oxford/AstraZeneca Vaccine: At the beginning of the pandemic, a viral vector vaccine, which is a gene technology product developed by transferring the genes encoding the spike proteins of SARS-CoV-2 into the non-replicating chimpanzee adenovirus, was produced in collaboration with the Oxford University and AstraZeneca (58,59). In the preclinical trials of the vaccine, high antibody levels were observed in pigs (8-59). Phase I/II studies of the vaccine, codenamed AZD1222, were conducted in England and South Africa, phase II/III studies were performed in England, and phase III studies were conducted in Brazil. A total of 23,848 volunteers aged >18 (7,548 from England and 4,088 from Brazil) participated in the four blinded, randomized controlled phase III study conducted in these three countries. In these studies, wherein vaccine efficacy was assessed based on symptomatic disease and polymerase chain reaction test, the vaccine was found to be effective against symptomatic COVID-19. As a result of the phase III trials, the efficacy rate was 62.1% in the group that received two full doses of vaccine, whereas it was 90% in the group that received half dose in the first dose and full dose at the second dose. Two doses of the vaccine are administered intramuscularly at 28 days apart (59). In the phase I/II study conducted with 1077 volunteers in England, the most common side effects associated with the vaccine were pain, fever, chills (shaking), muscle pain, headache, and weakness (58,59). Similar adverse effects were reported in phase II/III studies conducted in England, in two different centers with 560 patients, and no serious side effects were observed once again (58). Transverse myelitis developed in two individuals in the group that received two doses of the Oxford/AstraZeneca vaccine and in one individual in the control group that received meningococcal vaccine; however, no direct association with the vaccine was found (60).

Sputnik V (Gam-COVID-Vac): The Sputnik V vaccine, one of the first registered COVID-19 vaccines, was developed in Russia by the Gamaleya Institute. It is a vector vaccine developed by transferring the genes encoding the spike proteins of the SARS-CoV-2 genome into adenovirus type 26 at the first dose and adenovirus type 5 at the second dose. It was named Gam-COVID-Vac by Russia in August 2020. Sputnik V has now reached 61 countries as of December 2020, including Russia, Argentina, Belarus, Hungary, Serbia, and United Arab Emirates (61). Sputnik V, which was recognized as safe based on the results of phase I and II clinical trials, produced a high cellular and humoral immune response. Following that, in a double-blind randomized placebo-controlled study conducted in 25 clinics in Russia, 21,977 volunteers aged ≥18 years were assigned to the vaccinated group, whereas 5476 volunteers were assigned to the placebo group. The vaccine group received two doses of the vaccine at 21 days apart. The presence of COVID-19 at least 21 days following the first vaccination was assessed. COVID-19 was detected in 16 individuals (0.1%, n=14964) in the vaccinated group and in 62 individuals (1.3%; n=4902) in the placebo group; thus, its vaccine efficacy was 91.6%. The vaccine was 100% effective in preventing severe COVID-19 (62). Although mild and moderate local side effects were observed, no serious side effects were detected (62).

Johnson & Johnson (Ad26.COV2.S): This is a vaccine developed by delivering genes encoding spike proteins of SARS-CoV-2 virus via adenovirus type 26. It is the third COVID-19 vaccine to be approved for emergency use in the United States. The vaccine is administered intramuscularly as a single dose in individuals aged >18 years (63) Adverse effects and immune response were compared with the placebo group in a phase I/II trial wherein 402 volunteers aged 18-55 and >55 years were separated into two distinct cohorts. Although the most common local adverse effect is pain at the injection site, the most common systemic adverse effects were weakness, headache, and muscle pain. Neutralizing antibodies were detected in 90% of the participants 29 days after the first dose and 100% of them on day 57 (64). Phase III trials were conducted with 40,000 volunteers aged 18-100 years. Protective rates against symptomatic COVID-19 14 and 28 days after vaccination were 66.3% and 65.5%, respectively. The efficacy observed after 14 days varied by gender, age, race, and ethnic groups. The highest efficacy was 77% in the United States. Although some hospitalizations were associated with COVID-19 in 31 participants 14 days after the vaccination, 2 of them were in the vaccinated group, and no hospitalizations were noted in the vaccinated group 28 days after vaccination. The Janssen COVID-19 vaccine may be also protective against asymptomatic COVID-19 (63). Thrombocytopenia and cerebral venous sinus

thrombosis were reported in 42 women aged 18-49 years after receiving the Janssen vaccine for 1-2 weeks (60). The Centers for Disease Control and Prevention and FDA have warned against the risk of vaccine-induced thrombocytopenia and thrombosis, particularly in women aged 18-49 years (65).

Protein Subunit Vaccines

These vaccine types produce immunity by containing only the protein part of the virus without including the genetic material of the virus. Hepatitis B and pneumococcal vaccines are examples of protein subunit vaccines (66). There exist 38 vaccine candidates that are intended to produce immunity by transferring SARS-CoV-2 proteins to the human body using this method.

Novovax: Novavax, which is the first protein subunit vaccine to complete its phase III trial, was found to produce 89.7% protection in the original strain, as a result of a study conducted at 33 centers in the United Kingdom. Ten participants in the vaccinated group and 96 participants in the placebo group developed COVID-19 7 days after the second dose. Hospitalization and death were not observed in any of the 10 individuals who received the vaccine and subsequently became infected. Although a small number of mild and moderate adverse effects were observed, no serious adverse effects were detected (67).

Table 1 compares the characteristics of viral vector vaccines and protein subunit vaccines (67).

CONCLUSION

COVID-19 vaccines granted for EUA so far, are safe and effective. Vaccines are the most important tools in protection from the disease.

Development of new vaccines is still ongoing.

Table 1. Property of COVID-19 viral vector and protein subunit vaccines

Viral vector vaccines	**Advantage**	Faster and cheaper production		
	Disadvantage	Possibility of integrating the viral genome into the recipient genome, Low immune response in individuals who have previously encountered vector viruses		
	Other vaccines produced by this method	Hepatitis C, influenza, tuberculosis HIV vaccines		
Market name of vaccines	**Number of doses**	**Vaccine schedule (day)**	**Efficacy of vaccine**	**Developer country**
1. AstraZeneca, Oxford University (AZD1222, ChAdOx1)	2 doses 1. dose 1×(1/2) 2. dose 1×1	0, 28	90%	England
2. Sputnik V, Gamaleya Research Institute, Part of Russia's Ministry of Health (Gam-COVID-Vac)	2 doses	0, 21	91.6%	Russia
3. Janssen, Johnson & Johnson Pharmaceutical Company (Ad26. COV2.S)	2 doses	0, 56	74.4% (ABD) 64.7% (Latin America) 52% (South Africa)	ABD
	1 dose	0		
4. CanSino Biology, Military Academy of Medical Sciences (Ad5CoV)	1 dose	0	96-97%	China
Protein subunit vaccines	**Advantage**	Few side effects, Faster production		
	Disadvantage	Low immune response, booster vaccinatıon requirement		
	Other vaccines produced by this method	Pneumococcal vaccine, influenza, hepatitis B vaccine		
Market name of vaccines	**Number of doses**	**Vaccine schedule (day)**	**Efficacy of vaccine**	**Developer country**
1. Novavax (SARS-CoV-2 glycoprotein + matrix M)	2 doses	0, 21	89.7%	ABD
2. Medico Ing. (VLP)	2 doses	0, 21	-	Canada

HIV: Human immunodeficiency virus, COVID-19: Coronavirus disease-2019, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus 2, VLP: Virus like particles

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.A., H.R.S., M.R.D., S.Ar., F.Ş., Design: S.A., H.R.S., M.R.D., S.Ar., F.Ş., Data Collection or Processing: S.A., H.R.S., M.R.D., S.Ar., F.Ş., Analysis or Interpretation: S.Ar., F.Ş., Literature Search: S.A., H.R.S., M.R.D., S.Ar., F.Ş., Writing: S.A., H.R.S., M.R.D., S.Ar., F.Ş.

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REFERENCES

1. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science 2020;369:77-81.
2. Kyriakidis NC, López-Cortés A, González EV, Grimaldos AB, Prado EO. SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. NPJ Vaccines 2021;6:28.
3. Lee NH, Lee JA, Park SY, Song CS, Choi IS, Lee JB. A review of vaccine development and research for industry animals in Korea. Clin Exp Vaccine Res 2012;1:18-34.
4. Burrell CJ, Howard C, Murphy F, Burrell C, Howard C, Murphy F. Vaccines and vaccination. Fenner and White's Medical Virology 2017:155-67.
5. List of COVID-19 Vaccine Authorizations. Available from: https://en.wikipedia.org/wiki/List_of_COVID-19_vaccine_authorizations Accessed: 12 August 2021.
6. COVID-19 Vaccine Tracker. Available from: https://covid19.trackvaccines.org/agency/who/ Accessed: 12 August 2021.
7. Strategic Advisory Group of Experts on Immunization (SAGE) COVID-19 vaccines technical documents. Available from: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials Accessed: 12 August 2021.
8. Farma PB. Clinical Trial Report Interim II: A Phase III, Observer-blind, Randomized, Placebo-controlled Study of the Efficacy, Safety and Immunogenicity of SARS-CoV-2 Inactivated Vaccine in Healthy Adults Aged 18-59 Years in Indonesia. 2021.
9. Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. The Lancet. 2021.
10. Ella R, Reddy S, Blackwelder W, Potdar V, Yadav P, Sarangi V, et al. Efficacy, safety, and lot to lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): a, double-blind, randomised, controlled phase 3 trial. medRxiv. 2021. doi: 10.1101/2021.06.30.21259439.
11. Chen Y, Shen H, Huang R, Tong X, Wu C. Serum neutralising activity against SARS-CoV-2 variants elicited by CoronaVac. Lancet Infect Dis 2021;21:1071-2.
12. Wang GL, Wang ZY, Duan LJ, Meng QC, Jiang MD, Cao J, et al. Susceptibility of Circulating SARS-CoV-2 Variants to Neutralization. N Engl J Med 2021;384:2354-6.
13. Yu J, Tostanoski LH, Peter L, Mercado NB, McMahan K, Mahrokhian SH, et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. Science 2020;369:806-11.
14. Wolff JA, Malone RW, Williams P, Chong W, Acsadi G, Jani A, et al. Direct gene transfer into mouse muscle in vivo. Science 1990;247(4949 Pt 1):1465-8.
15. Duran T, Aydın Terzioğlu M, Çine N. Lipid nanoparçacık tabanlı mRNA aşı teknolojisi ve SARS-CoV-2 (COVID-19) mRNA aşıları. Canatan D, Alkan ŞŞ, editörler. Güncel COVID-19 Bilgileri. 1. Baskı. Ankara: Türkiye Klinikleri; 2021.p.47-56.
16. Verbeke R, Lentacker I, De Smedt SC, Dewitte H. Three decades of messenger RNA vaccine development. Nano Today 2019;28:100766.
17. Karikó K, Muramatsu H, Welsh FA, Ludwig J, Kato H, Akira S, et al. Incorporation of pseudouridine into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability. Mol Ther 2008;16:1833-40.
18. Kauffman KJ, Webber MJ, Anderson DG. Materials for non-viral intracellular delivery of messenger RNA therapeutics. J Control Release 2016;240:227-34.
19. Guan S, Rosenecker J. Nanotechnologies in delivery of mRNA therapeutics using nonviral vector-based delivery systems. Gene Ther 2017;24:133-43.
20. Kim J, Eygeris Y, Gupta M, Sahay G. Self-assembled mRNA vaccines. Adv Drug Deliv Rev 2021;170:83-112.
21. Midoux P, Pichon C. Lipid-based mRNA vaccine delivery systems. Expert Rev Vaccines 2015;14:221-34.
22. Zeng C, Zhang C, Walker PG, Dong Y. Formulation and delivery technologies for mRNA vaccines. In: Current topics in microbiology and immunology. Springer, Berlin, Heidelberg, 2020.
23. Sahay G, Alakhova DY, Kabanov AV. Endocytosis of nanomedicines. J Control Release 2010;145:182-95.
24. Van Nuffel AM, Benteyn D, Wilgenhof S, Pierret L, Corthals J, Heirman C, et al. Dendritic cells loaded with mRNA encoding full-length tumor antigens prime CD4+ and CD8+ T cells in melanoma patients. Mol Ther 2012;20:1063-74.
25. De Silva NS, Klein U. Dynamics of B cells in germinal centres. Nat Rev Immunol 2015;15:137-48.
26. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov 2018;17:261-79.
27. World Health Organization. Draft landscape of COVID-19 candidate vaccines. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines Accessed on August 24, 2021.
28. Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus. Fact sheet for healthcare providers administering vaccine. https://www.fda.gov/media/144413/download Accessed on August 23, 2021.
29. Emergency Use Authorization (EUA) of the Moderna COVID-19 Vaccine to prevent Coronavirus Disease 2019 (COVID-19). Factsheet for healthcare providers administering vaccine. https://www.fda.gov/media/144637/download?utm_medium=email&utm_source=govdelivery Accessed on August 12, 2020.
30. Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med 2020;383:2439-50.
31. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 Vaccine. N Engl J Med 2020;383:2603-15.

32. Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Six Month Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine. Available from: https://www.medrxiv.org/content/10.1101/2021.07.28.21261159v1.full.pdf

33. Wall EC, Wu M, Harvey R, Kelly G, Warchal S, Sawyer C, et al. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. Lancet 2021;397:2331-3.

34. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature 2021;596:276-80.

35. Edara VV, Pinsky BA, Suthar MS, Lai L, Davis-Gardner ME, Floyd K, et al. Infection and Vaccine-Induced Neutralizing-Antibody Responses to the SARS-CoV-2 B.1.617 Variants. N Engl J Med 2021;385:664-6.

36. Ohmit SE, Victor JC, Rotthoff JR, Teich ER, Truscon RK, Baum LL, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. N Engl J Med 2006;355:2513-22.

37. Plotkin S, Robinson JM, Cunningham G, Iqbal R, Larsen S. The complexity and cost of vaccine manufacturing - An overview. Vaccine 2017;35:4064-71.

38. Abu-Raddad LJ, Chemaitelly H, Butt AA; National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med 2021;385:187-9.

39. Lopez Bernal J, Andrews N, Gower C, Gallegher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med 2021;385:585-94.

40. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-07/07-COVID-Oliver-508.pdf (Accessed on July 23, 2021).

41. Chapin-Bardales J, Gee J, Myers T. Reactogenicity Following Receipt of mRNA-Based COVID-19 Vaccines. JAMA 2021;325:2201-2.

42. CDC COVID-19 Response Team; Food and Drug Administration. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14-23, 2020. MMWR Morb Mortal Wkly Rep 2020.

43. Shimabukuro T. COVID-19 vaccine safety update, Advisory Committee on Immunization Practices (ACIP) meeting, January 27, 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/06-COVID-Shimabukuro.pdf (Accessed on January 28, 2021).

44. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med 2021;385:187.

45. European Medicines Agency. EMA recommends COVID-19 Vaccine Moderna for authorisation in the EU. https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-moderna-authorisation-eu (Accessed on January 06, 2021).

46. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med 2020;383:1920-31.

47. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med 2020;383:2427-38.

48. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384:403-16.

49. Normark J, Vikström L, Gwon YD, Persson IL, Edin A, Björsell T, et al. Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination. N Engl J Med 2021.

50. Manisty C, Otter AD, Treibel TA, McKnight Á, Altmann DM, Brooks T, et al. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. Lancet 2021;397:1057-8.

51. Sangli S, Virani A, Cheronis N, Vannatter B, Minich C, Noronha S, et al. Thrombosis With Thrombocytopenia After the Messenger RNA-1273 Vaccine. Ann Intern Med 2021;L21-0244.

52. Kahraman EP, Altındiş M. COVID 19 Vaccines; Towards the end of the Pandemic? J Biotechnol and Strategic Health Res 2020;4:240-9.

53. Afrough B, Dowall S, Hewson R. Emerging viruses and current strategies for vaccine intervention. Clin Exp Immunol 2019;196:157-66.

54. Azap A. COVID-19 Vaccines: Light at the end of the Tunnel. Archives Medical Review Journal 2020;29:94-100.

55. Yavuz E. COVID-19 Vaccines. Türk Aile Hek Derg 2020;24:227-34.

56. Haque A, Pant AB. Efforts at COVID-19 Vaccine Development: Challenges and Successes. Vaccines (Basel) 2020;8:739.

57. World Health Organization. Draft landscape and tracker of COVID- 19 candidate vaccines. [Internet]. Switzerland : World Health Organization; 2021 [Access date: 24 Ağustos 2021]. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

58. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in youngand old adults (COV002): a single-blind, randomised,controlled, phase 2/3 trial. Lancet 2020;396:1979-93.

59. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single blind, randomised controlled trial. Lancet 2020;396:467-78.

60. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99-111. Erratum in: Lancet 2021;397:98.

61. Montalti M, Solda G, Di Valerio Z, Salussolia A, Lenzi J, Forcellini M, et al. ROCCA observational study: Early results on safety of Sputnik V vaccine (Gam-COVID-Vac) in the Republic of San Marino using active surveillance. EClinicalMedicine (2021):101027.

62. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. Safety and immunogenicity of an rAd26 and rAd5 vector based heterologous prime-boost Covid-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet 2021;397:671-81.

63. Oliver SE, Gargano JW, Scobie H, Wallace M, Hadler SC, Leung J, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Janssen COVID-19 Vaccine - United States, February 2021. MMWR Morb Mortal Wkly Rep 2021;70:329-32.

64. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med 2021;384:1824-35.

65. Centers for Disease Control and Prevention (CDC). Selected Adverse Events Reported after COVID-19 Vaccination. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html (Access date: 25 August 2021).

66. Ho, Gibaldi. Biotechnology and Biopharmaceuticals (Transforming Proteins and Genes intoDrugs). Hoboken, New Jersey: John Wiley & Sons, Inc. ISBN 0-471-20690-3 Copyrght© 2003.

67. Heath PT, Galiza EP, Baxer DN, Boffito M, Browne D, Burns F, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. New England Journal of Medicine, 2021.

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A Convenient Method of Improving Doctor-patient Communication in Hallux Valgus Surgery: Visual Animations

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Abstract

Objective: This study aimed to investigate the effects of using visual animation on the informed consent for hallux valgus surgery, patient awareness, and patient satisfaction.

Methods: This study included 42 patients with hallux valgus for whom distal metatarsal osteotomy surgeries were planned. During the informed consent process, the patients were informed verbally and in writing. Their knowledge levels were measured using open-ended questions. An animated video, which included disease findings and steps of the planned surgery, was shown to the patients after 28 days on average. The effects of the visual animation on the knowledge levels of the patients and on the satisfaction levels with the patient-doctor communication were examined. Data were analyzed statistically.

Results: Although the animated video provided information on hallux valgus deformity and distal metatarsal osteotomy, patients expressed a better understanding of surgical complications and other treatment options. Video animation significantly increased the knowledge and satisfaction levels of the patients ($p=0.001$; $p<0.01$, respectively).

Conclusion: Video animations that provide patients with easily accessible, inexpensive, reproducible, permanent, impressive, and understandable audiovisual information about diseases may be applied in obtaining informed consent and in improving patient-doctor communication.

Keywords: Video animation, informed consent, hallux valgus

INTRODUCTION

Hallux valgus is a common condition and reduces the life quality of the patients. In general, surgery is recommended for patients with moderate or severe deformities and in symptomatic cases (1). Over 100 surgical procedures have been described for hallux valgus surgery (2,3). As no surgical approach has been established as the gold standard for hallux valgus, the surgical complication rate reaches 15% (4). Patients with hallux valgus are also at risk of postoperative complications; thus, they should be informed correctly and adequately about the treatment.

Surgeons have an ethical and legal obligation to provide patients with adequate information about the risks, benefits, and alternatives of invasive procedures in the surgeon-patient interview and in the informed consent process (5).

In situations where the number of patients per doctor is high, the time allocated for the patient may be limited. However, doctor-patient communication may be affected by the sociocultural beliefs of the patients, use of unfamiliar medical terms, use of foreign language, and illiteracy. To address these difficulties, simple, fast, understandable, and repeatable communication methods are needed to improve doctor-patient communication.

This study aimed to examine the effects of using three-dimensional animated videos supported by a tablet PC to explain hallux valgus findings and surgical procedures on the informed consent process and patient satisfaction.

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METHODS

The study was approved by the Clinical Research Ethics Committee (dated: 15.01.2016, decision no: 757). A total of 42 patients who were diagnosed with hallux valgus between February 2016 and November 2018, who were not relieved of their complaints with conservative treatments, and who were planned for distal metatarsal osteotomy surgery were included in the study after their informed consent forms were received.

The gender, age, educational status, diagnosis, and planned surgery data of the patients were recorded. Patients were informed verbally and in writing about the surgery, surgery-specific complications, diagnoses, disease findings, stages of the planned surgery, and treatment options other than the planned surgery in the polyclinic conditions. For objective evaluation, six items were prepared for each information (3,6-9). After a verbal and written explanation, patients were asked open-ended questions to determine their knowledge levels (5,10-12). Correct answers to each open-ended question were scored 0-6 points according to the information provided previously. Patients who provided incorrect responses scored 0, and those with correct answers in all six items were given 6 points.

Patients who received surgery appointments were taken to the orthopedic unit after 28 (15-65) days on average. An animated video that included the findings of the disease and steps of the planned surgery was shown to the patients in the unit (Ankle & Foot Pro III 3.8.1 and Complete Orthopedic version 1.1.1 3D4 Medical's NOVA3 Technology) through a tablet PC (iPad Wi-Fi 128GB Black; Apple Inc., CA, USA) (Figure 1).

Although explanations were not included in the animated video, explanations were given about other treatment options and surgery-related complications. Patients were asked again with the same open-ended questions to determine their knowledge levels after they have watched the animation. The knowledge level after watching the animation was also scored 0-6 points. Patients scored 0 points if they did not know any of the items asked and 6 points if they knew all of them.

In addition, the satisfaction with the written-oral informed consent form and animated video and informed consent form was scored 0-6 points. Data obtained were compared statistically.

Statistical Analysis

The Number Cruncher Statistical System 2007 (Kaysville, UT, USA) program was employed for statistical analyses. Wilcoxon signed-rank test and descriptive statistical methods (mean, standard deviation, median, frequency, percentage, and minimum-maximum values) were employed to compare quantitative data. In the intragroup comparisons of the study variables, which did not show a normal distribution, the Wilcoxon signed-rank test was employed. The significance level was taken as $p<0.01$ and $p<0.05$.

RESULTS

Demographic features of the participants are shown in Table 1. Significant increases were detected in the knowledge level on the disease findings, surgery steps, other treatment options, surgery-related complications, and satisfaction with the use of animation in obtaining informed consent (Table 2) ($p=0.001$; $p<0.01$).

DISCUSSION

This study focused on the effect of using visual animation on the informed consent process in patients with hallux valgus, for whom distal metatarsal osteotomy was planned as treatment. In this study, the use of visual animations increased the knowledge and satisfaction levels of the patients about the topic.

Hallux valgus is more common in women, the function of the foot is disrupted, and patients are anxious about the postoperative appearance of the foot (9). This situation increases the expectation in the hallux valgus surgery, which is already at risk of complications (9,13). Thus, the surgeon must fully inform the patient in a sufficient, accurate, and understandable manner to relieve the patients of their anxiety.

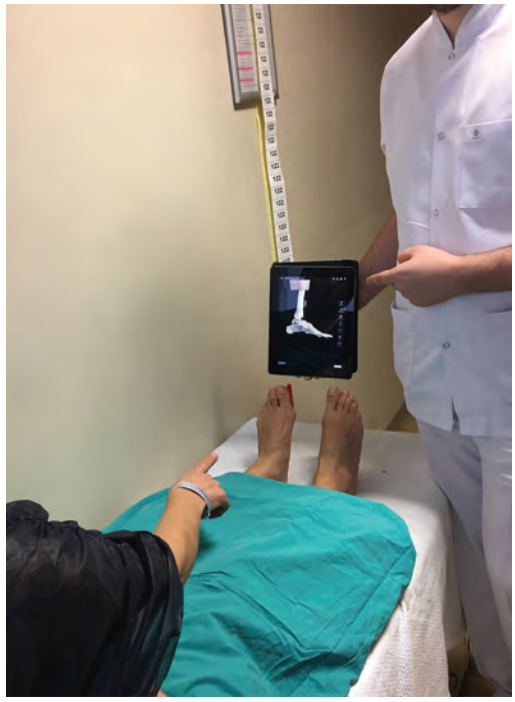

Figure 1. Method of showing visual animations to the patients

Patients have the right to demand verbal or written explanations of their diagnoses, treatment, benefits and possible risks of surgical treatment, alternative treatment methods, disease progression, and expected outcomes if they reject the treatment (10). However, in current practice, patients cannot receive sufficient information on the surgical procedures from doctors, nurses, and other healthcare staff (14,15). This situation results in doubts, fear, or anxiety in the patients about establishing a relationship with the healthcare staff, and they might approach the surgical process and relevant outcomes with fear (12,16).

The facilitated access to information in parallel with recent technological developments has substantially improved the patient-doctor relationship (17). The true-false information that patients obtained from the internet before consulting with the doctor affects the transfer of information from the doctor to the patients (18). Although patients were passive in the past about their decisions related to their treatments, they have now become more active (19,20). This situation requires that patients receive accurate information about their treatment (18,21).

A study that investigated how much patients were informed before their surgeries reported that nearly one-fourth of these patients were not informed at all, nearly one-fifth did not know their diagnoses, and more than half did not know their surgical procedures. Moreover, 12% and 14% of the patients stated that they were not informed of the complications that might occur during and after surgery, respectively. The study emphasized that verbal and written information was insufficient and that the use of visual materials such as videos and photos is necessary to inform patients (22).

A previous study discussed the effects of several methods applied to inform patients, such as plain texts, animated videos, audio-video slideshows, cartoons, and narration. The knowledge levels of the participants were measured after they received information using these methods. As a result, the study reported that the knowledge levels of the patients increased with the use of audio and video animations and audio slideshows (23). In another study that used verbal presentations, brochures, and computer-aided multimedia methods on the informed

Table 1. Demographic features of the patients

		Minimum-maximum	Average ± SD
Age (years)		26-62	48.30±10.96
		n	**%**
Gender	**Female**	35	83.3
	Male	7	16.7
Education	**Literate**	10	23.8
	Primary school	12	28.6
	Secondary school	7	16.7
	High school	5	11.9
	University	8	19.0

SD: Standard deviation

Table 2. Changes in the information and satisfaction levels before and after showing the animation video

		Verbal-written consent	Consent with animation	Percentage of the change	[a]p
Knowledge on the disease findings	Average ± SD	2.60±0.59	4.81±0.71	92.66±43.09	**0.001****
	Min-max (median)	2-4 (3)	4-6 (5)		
Knowledge on the planned surgery steps	Average ± SD	2.52±0.74	5.21±0.78	117.74±51.91	**0.001****
	Min-max (median)	2-5 (2)	2-6 (5)		
Knowledge on other treatment options	Average ± SD	2.86±0.47	3.50±0.55	27.18±35.74	**0.001****
	Min-max (median)	2-4 (3)	3-5 (3)		
Knowledge on the complications	Average ± SD	2.67±0.53	3.55±0.67	37.30±33.90	**0.001****
	Min-max (median)	2-4 (3)	3-5 (3)		
Satisfaction level	Average ± SD	4.83±0.76	5.91±0.37	24.88±19.77	**0.001****
	Min-max (median)	4-6 (5)	4-6 (6)		

[a]Wilcoxon signed-rank test, **p<0.01, Min: Minimum, Max: Maximum, SD: Standard deviation

consent process, the status of remembering the information was measured by asking patients on the surgery day and 6 weeks after the surgery. As a result, 88% of the patients in the verbal presentation group, 76% in the brochure group, and 98% in the multimedia group provided correct answers. In the evaluation performed after 6 weeks, the permanence of the information and the satisfaction with it was high in the multimedia group (24).

We believe that understanding and learning information is easier with audiovisual materials because of their interesting and stimulating nature. In the present study, significant increases were found in the knowledge levels of the patients on disease findings, planned surgery type, alternative treatment methods, and complications after the animate video was introduced.

Although the animated video provided information only on the disease findings and surgical procedures, patients expressed a better understanding of other treatment methods and complications.

In a study that examined the effects of providing visual information on the anxiety before surgery in patients with arthritis, a 4-min video that described joint lavage was shown to one patient group, whereas no video was shown to the other group. Compared with the group without the video, the group that watched the video had lower anxiety before surgery and had significantly higher tolerability of the procedure (25). Although no numerical evaluations were made on anxiety in our study, we believe that visual animations decreased the anxiety of the patients before surgery. After they have watched the animation, none of the patients declined the planned surgical treatment and a significant increase was found in the satisfaction scores of these patients. In addition, the animation method was time efficient, as the video did not exceed 2 min. Moreover, since the animations showed the 3D structure of the tissues, they provided clearer images and information than the standard video images.

Study Limitations

This study has some limitations. First, following our literature review, we did not found any visual animation applications explaining other treatment options for hallux valgus deformity and complications about distal metatarsal osteotomy; thus, we could not provide our patients with visual animations in this context. We believe that this limitation is also applicable to visual animation designers. Second, the relation of providing information through visual animation with education, gender, and age of the patients could not be examined because of the small number of patients. Third, the same group of patients received a written/verbal explanation and visual animation. We could not form a control group because of the inadequacy of cases. Fourth, although the interval between applications was nearly 1 month, recall bias is still possible. Finally, we found it inappropriate to inform the patients only with visual animations, which is outside the standard application, in medicolegal terms. These limitations might be addressed in studies with larger patient groups.

CONCLUSION

The results of this study suggest that obtaining informed consent is not only a simple step but an important process in patient-doctor communication. This process must be managed as accurately as the surgery itself. In the present technological age, nearly every doctor owns a smartphone or a smart tablet PC, and many hospitals use electronic healthcare information systems. Visual animation applications providing audiovisual data to patients and doctors may be uploaded to these smart devices and adapted to the healthcare information system easily. We believe that visual animation applications, which are easily understood, accessible, and reproducible and provide permanent and impressive audiovisual information in patient-doctor communication by avoiding difficult medical terms, must be a standard procedure for the informed consent process.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee (dated: 15.01.2016, decision no: 757).

Informed Consent: Consent form was obtained.

Peer-review: Externally peer-reviewed.

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REFERENCES

1. Şahin N, Cansabuncu G, Çevik N, Türker O, Özkaya G, Özkan Y. A randomized comparison of the proximal crescentic osteotomy and rotational scarf osteotomy in the treatment of hallux valgus. Acta Orthop Traumatol Turc 2018;52:261-6.
2. Klugarova J, Hood V, Bath-Hextall F, Klugar M, Mareckova J, Kelnarova Z. Effectiveness of surgery for adults with hallux valgus deformity: a systematic review. JBI Database System Rev Implement Rep 2017;15:1671-710.
3. Song JH, Kang C, Hwang DS, Lee GS, Lee SB. Comparison of Radiographic and Clinical Results After Extended Distal Chevron Osteotomy With Distal Soft Tissue Release With Moderate Versus Severe Hallux Valgus. Foot Ankle Int 2019;40:297-306.

4. Lai MC, Rikhraj IS, Woo YL, Yeo W, Ng YCS, Koo K. Clinical and Radiological Outcomes Comparing Percutaneous Chevron-Akin Osteotomies vs Open Scarf-Akin Osteotomies for Hallux Valgus. Foot Ankle Int 2018;39:311-7.
5. Lin YK, Chen CW, Lee WC, Cheng YC, Lin TY, Lin CJ, et al. Educational video-assisted versus conventional informed consent for trauma-related debridement surgery: a parallel group randomized controlled trial. BMC Med Ethics 2018;19:23.
6. Hecht PJ, Lin TJ. Hallux valgus. Med Clin North Am 2014;98:227-32.
7. Raikin SM, Miller AG, Daniel J. Recurrence of hallux valgus: a review. Foot Ankle Clin 2014;19:259-74.
8. van Groningen B, van der Steen MC, Reijman M, Bos J, Hendriks JG. Outcomes in chevron osteotomy for Hallux Valgus in a large cohort. Foot (Edinb) 2016;29:18-24.
9. Kromuszczyńska J, Kołodziej Ł, Jurewicz A. Wound healing complications in patients with and without systemic diseases following hallux valgus surgery. PLoS One 2018;13:e0197981.
10. Michalski A, Stopa M, Miśkowiak B. Use of Multimedia Technology in the Doctor-Patient Relationship for Obtaining Patient Informed Consent. Med Sci Monit 2016;22:3994-9.
11. Braddock CH 3rd, Edwards KA, Hasenberg NM, Laidley TL, Levinson W. Informed decision making in outpatient practice: time to get back to basics. JAMA 1999;282:2313-20.
12. Egekeze N, Dubin J, Williams K, Bernhardt M. The Age of OrthoInfo: A Randomized Controlled Trial Evaluating Patient Comprehension of Informed Consent. J Bone Joint Surg Am 2016;98:e81.
13. Robinson C, Bhosale A, Pillai A. Footwear modification following hallux valgus surgery: The all-or-none phenomenon. World J Methodol 2016;6:171-80.
14. Ghulam AT, Kessler M, Bachmann LM, Haller U, Kessler TM. Patients' satisfaction with the preoperative informed consent procedure: a multicenter questionnaire survey in Switzerland. Mayo Clin Proc 2006;81:307-12.
15. Carmi A, Cotler M, Fluss SKG. The UNESCO Chair in Bioethics, Informed Consent. Israel: Faculty of Law, University of Haifa. 2003.
16. Wysong PR, Driver E. Patients' perceptions of nurses' skill. Crit Care Nurse 2009;29:24-37; quiz following 37.
17. Bowers N, Eisenberg E, Montbriand J, Jaskolka J, Roche-Nagle G. Using a multimedia presentation to improve patient understanding and satisfaction with informed consent for minimally invasive vascular procedures. Surgeon 2017;15:7-11.
18. Billon L, Décaudin B, Pasquier G, Lons A, Deken-Delannoy V, Germe AF, et al. Prospective assessment of patients' knowledge and informational needs and of surgeon-to-patient information transfer before and after knee or hip arthroplasty. Orthop Traumatol Surg Res 2017;103:1161-7.
19. Bernstein J, Kupperman E, Kandel LA, Ahn J. Shared Decision Making, Fast and Slow: Implications for Informed Consent, Resource Utilization, and Patient Satisfaction in Orthopaedic Surgery. J Am Acad Orthop Surg 2016;24:495-502.
20. Slover J, Shue J, Koenig K. Shared decision-making in orthopaedic surgery. Clin Orthop Relat Res 2012;470:1046-53.
21. Abu Al-Rub Z, Hussaini M, Gerrand CH. What do patients know about their joint replacement implants? Scott Med J 2014;59:158-61.
22. Kurt E, Ucar M, Atac A. Quality of an Informed Consent Prior to a Surgical Intervention? Experience of a Teaching Hospital. Pak J Med Sci 2016;32:206-10.
23. Kraft SA, Constantine M, Magnus D, Porter KM, Lee SS, Green M, et al. A randomized study of multimedia informational aids for research on medical practices: Implications for informed consent. Clin Trials 2017;14:94-102.
24. Cornoiu A, Beischer AD, Donnan L, Graves S, de Steiger R. Multimedia patient education to assist the informed consent process for knee arthroscopy. ANZ J Surg 2011;81:176-80.
25. Ayral X, Gicquere C, Duhalde A, Boucheny D, Dougados M. Effects of video information on preoperative anxiety level and tolerability of joint lavage in knee osteoarthritis. Arthritis Rheum 2002;47:380-2.

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Cerclage Cable and Long Proximal Femoral Nail Antirotation Fixation in Treatment of Subtrochanteric Fractures: Functional and Radiological Outcomes and Complications

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Abstract

Objective: We aimed to present the radiological and functional outcomes and complications of intramedullary nailing with long proximal femoral nail antirotation (PFNA) and cerclage cable for spiral and oblique subtrochanteric femoral fractures.

Methods: The study included patients who underwent intramedullary nailing with long PFNA and cerclage cable due to closed, isolated, and spiral/oblique subtrochanteric femoral fractures and were followed up for at least one year. Fracture union was evaluated with anteroposterior and oblique radiographs of patients obtained at 2, 4, 6, and 12 months, postoperatively. Functional evaluation was done using lower extremity functional scale (LEFS) and visual analog scale (VAS).

Results: The mean time to union was 20.16±2.8 (range: 16-28) weeks, mean LEFS score of the patients was 74.08±2.3 (range: 70-80), and LEFS percentage was calculated as 92.75±16.20 (range: 88-100). Radiological evaluation of the reduction quality revealed that good results were acquired in 28 (84.8%) patients, whereas acceptable results were acquired in five (15.2%). The mean VAS score was 0.84±1.17 (range: 0-4). Radiological and clinical union was achieved in 32 (97%) patients within 6 months and union was achieved with some delay in one patient (3%) within 7 months

Conclusion: Subtrochanteric femur region is an area that is subject to complications due to its anatomic position and functional characteristics. The treatment for spiral/oblique subtrochanteric femur fractures with PFNA and cerclage cable is a reliable method that increases the stability of the fixation, allows early mobilization and weight bearing, and helps in the acquisition of satisfactory radiological and functional results.

Keywords: Subtrochanteric femur, cable cerclage, fracture, union

INTRODUCTION

The subtrochanteric region of the femur is defined as the junction of proximal and middle one-third of the femur or 5 cm distal to the inferior border of the lesser trochanter (1-3). Fractures in this region show bimodal distribution and occur as a result of a high-energy trauma in young individuals and low-energy trauma in the elderly, accounting for 7-24% of all hip fractures (1,2,4-6). It is one of the areas in the body that are

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exposed to high tensile and compressive forces (7). In displaced fractures of the subtrochanteric femur, proximal fragment is most commonly abducted, externally rotated, and flexed due to the effects of muscles attached to the proximal femur (6); thus, resulting in first entry problems or malreduction at the level of greater trochanter in intramedullary nail treatment (8).

Dynamic hip screw, proximal femur anatomic plate, and intramedullary nailing are used in the treatment (2,5,9). Anatomic reduction and sustainable rigid fixation are the main targets for treating subtrochanteric femur fractures. Stability, which is adequate to resist deformation and compression during weight bearing, must be ensured. Implant failure leading to shortness, non-union, and deformities can cause severe problems.

Subtrochanteric femur fractures are very difficult to treat; therefore, it is pertinent to discuss standard treatment methods. Better reduction can be achieved with open technique. However, evacuation of the fracture hematoma, extensive soft tissue injury, and periosteal stripping impairs fracture union. Soft tissue biology is less damaged in intramedullary fixation than in open reduction. Biomechanically, intramedullary fixation is regarded as the most advantageous treatment method (10,11). Auxiliary indirect reduction techniques are frequently employed before performing permanent fixation. Some of these methods include reduction clamps, Schanz screws, blocking screws, sharp, and ball-tipped pushers (4-7,12-15). Recently, cerclage or cable applications have been widely used to increase the stability of a fixation (1,9,14). Their use was controversial because it was thought to negatively affect the vascularity of the trochanteric region. However, recent studies have shown that cerclage application does not impair microvascular circulation (16-18).

In subtrochanteric femur fractures, the fixation method should have minimal impairment of the biological healing process and should allow early weight bearing and mobilization. Therefore, intramedullary nailing is the most preferred treatment method. Intramedullary nailing alone does not have sufficient stable fixation, which leads to serious complications (3,19,20). Thus, we aimed to present the efficacy of cerclage cable application as an adjunct to intramedullary nailing in terms of functional and radiological outcomes and complication, such as malunions and non-unions in patients with spiral/oblique subtrochanteric femur fractures extending to the metaphysis.

METHODS

A total of 33 patients who underwent fixation with long proximal femoral nail antirotation (PFNA) and cerclage cable method due to isolated spiral/oblique subtrochanteric femur fracture between January 2010 and January 2017 were included in the study. Prospectively recorded patient data were retrospectively analyzed. The study was conducted at our hospital and informed consent was preoperatively obtained from all the study patients. Approval for the study was granted by University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital Ethics Committee (approval no: 37732058-514.10). The study included patients who underwent long PFNA (Synthes) and cerclage cable application due to closed, isolated, and spiral/oblique subtrochanteric femur fractures and who were followed up for at least one year. Patients with a pathological fracture, open fracture, or concomitant fracture were excluded from the study. Of the 40 patients who met the inclusion criteria, 33 who completed regular follow-ups and attended the final examination were included in the study; two patients died during the follow-up period and two others could not be contacted. All patients with trochanteric fractures in whom fixation was considered as a treatment option underwent three-dimensional computed tomography (CT) for preoperative evaluation.

Demographic data, including age, sex, fracture side, trauma etiology, time from admission to surgery, operation time, fluoroscopy time, and follow-up duration, were recorded. Fractures were classified according to the AO/OTA classification system (21). Fracture union was evaluated postoperatively using anteroposterior and side/oblique radiographies of the patients at 2nd, 4th, 6th, and 12th months. The formation of callus tissue in three out of four cortices was considered as a union. Cases with no signs of union at 6 months were recorded as non-union and those with incomplete union were recorded as delayed union. Reduction quality (shortness, angulation, and rotation) was evaluated according to the modified criteria (cortical displacement <4 mm and angulation 10°: Good, acceptable, and poor) of Baumgaertner et al. (22,23). Functional evaluation was done using the lower extremity functional scale (LEFS) (24) and visual analog scale (VAS) (25). To avoid bias, patients were evaluated by a surgeon that is different from the operating surgeon. The presence of infection, shortness, deformation, reoperation, implant failure, and implant extraction observed during the follow-up period was noted.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 25.0 (SPSS Inc., Chicago, Illinois, USA). Data are presented as number, percentage, average, standard deviation, median, and range. Compliance of the data to normal distribution was evaluated by Shapiro-Wilk test. Data were then analyzed by Mann-Whitney U test and Spearman correlation test as appropriate. Statistical significance value set as $p<0.05$.

Surgical Method and Postoperative Protocol

Patients were operated on a fluoroscopy table in a lateral decubitus position. A total of 20 patients received regional anesthesia, whereas 13 patients received general anesthesia. Preoperatively, all the patients received 2 grams of first generation cephalosporin. The fluoroscopy device was placed perpendicular to the operating table, with the C-arm positioned above the patient. Anteroposterior views were taken in controlled traction. Following the confirmation of the region to which a cable was to be applied from the lateral aspect of the fracture line via fluoroscopy, approximately 3-5 cm incision was performed. The tensor fascia lata was dissected in an L-shaped fashion to reach the fracture, with minimum soft tissue damage and blunt dissection. After the fracture reduction was done with reduction forceps, cerclage cable fixation in adequate tension was done with one or more cerclage cables according to the shape and length of the fracture. Afterward, PFNA was inserted under fluoroscopic control and a thick K wire was advanced to the femoral neck over the proximal guide. Anteroposterior position of the K wire was confirmed by fluoroscopy. Lateral fluoroscopic images were obtained in internal and external rotations, with the hip flexed 90° and abducted 45°. Centralization or anteversion-retroversion of the K wire was confirmed using lateral images. Gamma nail of appropriate length was placed on the neck of the femur and compression was performed. All distal locking screws were statically locked. Fracture stabilization was evaluated by continuous fluoroscopy after completion of the fixation. The patients walked with the aid of a walker or crutches on the postoperative first day. Knee and hip range of motion and strengthening exercises were started after the second week. After the observation of radiological union, unassisted weight bearing was allowed.

RESULTS

Of the total patients included in the study, 16 were male and 17 were female. The mean age was 49.84±17 (range: 22-78) years. The fracture was on the right side in 18 (54.5%) patients and on the left side in 15 (45.5%) patients. Etiologically, the cause of fracture was traffic accident in 13 (39.4%) patients and falling from a height in 20 (60.6%) patients. According to the AO/OTA fracture classification, 21 (63.6%) patients had 31A3.1 type fracture and 12 (36.4%) patients had 31A1.3 type fracture. When the fracture patterns were examined, 14 (42.4%) patients had oblique fractures and 19 (57.6%) had spiral fractures. The mean operation time was 90.6±18.36 (range: 50-120) min. The mean fluoroscopy time during the surgery was 127.36±78.55 (range: 34-321) seconds. The mean follow-up duration was 42.15±16.20 (range: 12-80) months.

The mean union time was 20.16±2.8 (range: 16-28) weeks. The mean LEFS score of the patients was 74.08±2.3 (range: 70-80) and LEFS percentage was calculated as 92.75±16.20 (range: 88-100). The mean tip-apex distance was radiologically measured as 17.33±3.24 (range: 12-24) mm. Eleven patients developed shortness of the average 0.97±1.46 (range: 0-4) mm, whereas 22 patients did not develop shortness. Radiologically, 27 patients had no sagittal deformity, whereas 0.42±1.54 (range: -4-+4) sagittal angulation was observed in six patients. Radiologically, there was no coronal deformity in 26 patients, whereas 0.60±1.63 (range: -3-+4) coronal angulation was seen in seven patients. According to the radiological reduction quality evaluation criteria of Baumgaertner et al. (22,23) good results were achieved in 28 (84.8%) patients and acceptable results were obtained in five (15.2%). The mean VAS score was 0.84±1.17 (range: 0-4). Radiological and clinical union was achieved in 32 (97%) patients within 6 months (Figure 1) and union was achieved with some delay in one patient (3%) within 7 months. Serous discharge continuing for 3 weeks following the surgery was observed in one patient, whereas superficial infection, which was healed by antibiotic administration, was observed in two (Table 1). There were no patients with implant failure and implant breakage. There was no reduction loss that required reoperation. There was no statistical correlation between the fracture type and pattern and union time, operation time, and fluoroscopy time ($p>0.05$) (Table 2). There was no statistically significant relationship between the tip-apex distance and shortness, union time, and angulation ($p>0.05$) (Table 3).

DISCUSSION

Subtrochanteric spiral/oblique fractures are difficult to treat and rehabilitate. There is still debate over the optimal treatment method. Open reduction and internal fixation allows better visualization of the fracture and achievement of anatomic reduction; it has also minimized the risk of shortness. Extensive soft tissue injury, periosteal stripping, and evacuation of the fracture hematoma results in damage to the biological environment that is necessary for fracture healing. Anatomic reduction can be achieved with the use of plates as the fixation material. However, it has been reported that plates provide less mechanical performance compared to intramedullary fixation materials (26,27). Intramedullary fixation methods are biomechanically superior in the treatment of subtrochanteric fractures. However, a disadvantage of this method is the indirect reduction of the fracture. Indirect reduction is performed using a closed procedure with Schanz screws, blocking screws, and

Table 1. Demographic, functional, and radiological data of patients	
Gender; n (%)	
Male/female	17 (51.5%)/16 (48.5%)
Side	
Right/left	18 (54.5%)/15 (45.5%)
Etiology; n (%)	
Traffic accident	13 (39.4%)
Falling from a height	20 (60.6%)
Age;	
Mean (min-max) SD	49.85±17.08 (min-max: 22-78)
AO/OTA classification; n (%)	
31A1.1	21 (63.6%)
31A1.3	12 (36.4%)
Fracture pattern; n (%)	
Spiral	19 (57.6%)
Oblique	14 (42.4%)
Baumgartner reduction quality; n(%)	
Good	28 (84.8%)
Acceptable	5 (15.2%)
Operation time	
[Minutes; mean (min-max) SD]	90.6±18.36 (min-max: 50-120)
Fluoroscopy time	
[Seconds; mean (min-max) SD]	127.36±78.55 (min-max: 34-321)
VAS score;	
Mean (min-max) SD	0.84±1.17 (min-max: 0-4)
Radiological union time (weeks);	
Mean (min-max) SD	20.16±2.8 (min-max: 16-28)
LEFS;	
Mean (min-max) SD	74.08±2.3 (min-max: 70-80)
LEFS (%);	
Mean (min-max) SD	92.75±16.20 (min-max: 88-100)
Follow-up time	
[Months; mean (min-max) SD]	42.15±16.20 (min-max: 12-80)
Tip-apex distance (mm);	1
Mean (min-max) SD	7.33±3.24 (min-max: 12-24)
Shortness (mm);	
Mean (min-max) SD	0.97±1.46 (min-max: 0-4)
Sagittal angulation (°);	
Mean (min-max) SD	0.42±1.54 (min-max: -4-/+4)
Coronal angulation (°);	
Mean (min-max) SD	0.60±1.63 (min-max: -3/+4)
Complication; n (%)	
No	29 (87.9%)
Serous drainage	1 (3%)
Superficial infection	2 (6.1%)
Delayed union	1 (3%)

AO/OTA: Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association, VAS: Visual analog score, LEFS: Lower extremity functional scale, SD: Standard deviation, max: Maximum, min: Minimum

pointed and ball-tipped pushers. Reduction forceps and cerclage cable can be used with a minimally invasive procedure (28).

The effect of deforming muscle forces can cause incorrect positioning of the trochanteric entry and malreduction of the fracture. Malreduction (inability to achieve apposition of the fracture fragments, shortness, or rotation) can cause catastrophic complications, such as malunion, non-union, shortness, and deformation.

The main purpose of treating subtrochanteric spiral/oblique femur fractures is to achieve anatomic and sustainable stable fixation. Rigid fixation must be performed to allow early weight bearing and rehabilitation. It has been reported that intramedullary nail fixation without the use of cerclage cable in unstable comminuted subtrochanteric fractures results in 100% failure due to cyclic weight bearing; it also results in the displacement of the fracture gap with varus deformity and cut-out. Although cerclage cable application is an invasive method, its use is recommended because it provides medial support and prevents fixation failure in complex fractures (11).

The use of cerclage cables has been controversial until recent years because they were thought to disturb the microvascular circulation of the bone, thereby delaying bone union. In experimental and cadaveric studies, it was shown that the vascular support of the periosteum is circular and not longitudinal (14,16). It is supplied by many vascular sources, including recurrent vessels (16). Moreover, it was stated that angiogenesis in the bone proceeds in a centripetal direction and thus cerclage knot around the bone should cause minimal microvascular impairment (29). Minimally invasive percutaneous cerclage application causes minimal damage to the femoral perforating veins. The formation of anastomoses provides sufficient circulation (8). It was shown that non-union can be prevented by minimal soft tissue dissection and periosteal stripping with percutaneous cerclage cable application (14).

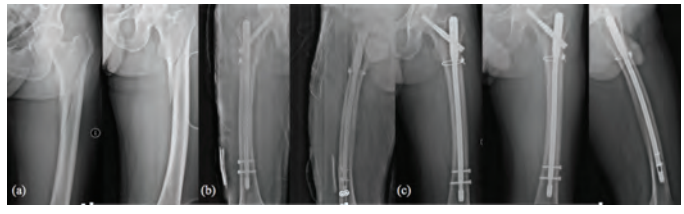

Figure 1. A 39 years old male patient was treated with a mini open cerclage and a long proximal femoral nail for a 31A3.3 type fracture of the left hip due to a fall from a height. Preoperative anteroposterior and optimal lateral oblique direct radiographs (a), postoperative day 1 anteroposterior and lateral femur direct radiographs (b), postoperative 1 year postoperative anteroposterior, oblique, and lateral radiographs (c)

Table 2. Statistical analysis of fracture type and pattern with time of operation, time of fluoroscopy, and time of union				
		Operation time	**Fluoroscopy time**	**Union time**
AO/OTA (Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association) fracture type				
31A1.1	Min-max (median)	50-120 (90)	34-321 (140)	16-28 (20)
	Mean ± SD	92.4±20.0	149.1±77.3	20.0±3.2
31A1.3	Min-max (median)	60-110 (90)	44-296 (79)	18-24 (20)
	Mean ± SD	87.5±15.4	89.3±67.9	20.5±2.1
Fracture pattern	**p**	0.437	0.008	0.408
Spiral	Min-max (median)	50-120 (90)	34-321 (85)	16-24 (20)
	Mean ± SD	89.5±18.4	113.2±79.5	20.5±2.4
Oblique	Min-max (median)	60-120 (90)	52-301 (138.5)	16-28 (18)
	Mean ± SD	92.1±18.9	146.6±75.7	19.7±3.3
	p	0.754	0.122	0.203

Mann-Whitney U test and Spearman correlation test, AO/OTA: Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association, max: Maximum, min: Minimum, SD: Standard deviation

Table 3. Correlation between type-apex distance and shortness, sagittal angulation, coronal angulation, and union time				
	Shortness	**Sagittal angulation**	**Coronal angulation**	**Union time**
Tip-apex distance				
r	0.043	0.213	0.023	-0.117
p	0.811	0.233	0.898	0.724
Mann-Whitney U test and Spearman correlation test				

However, cerclage cabling can cause cortical damage and bone resorption with the effect of micromovements (14). Braided cerclage cables decrease the implant-bone contact surface and increase stability (30).

There is a risk of damage to the superficial femoral artery and vein during cerclage cable application (17,31). In *in vitro* CT angiographic evaluation, relatively safe zones were described, particularly for shaft fractures (31,32). The concepts of a safe zone for trochanteric region, number of cerclages that could be applied, and distance between cerclages remain controversial. We applied cerclage cable in all the patients using a minimally invasive method, with minimal soft tissue dissection and periosteal stripping. The cable was inserted after reduction was done with reduction forceps and confirmed by fluoroscopy. No cable-related complications were observed during and after the surgery.

In a study by Codesido et al. (3), patients who had open reduction intramedullary nail and cerclage wire fixation had a mean union time of 4.35±1.75 months, mean incision length of 18.30±4.51, and mean operation time of 100.69±28.12 minutes; complications were observed in one patient (3.3%) and reduction success was evaluated as good in 29 (96.7%), acceptable in one (3.3%), and poor in no patients (0%). In a study by Gong et al. (26), it was reported that the mean union time was 20 (range: 16-24) weeks and that the mean operation time was 105 (range: 85-135) min; there were no major complications, such as non-union, malunion, and implant failure. It was stated that good and perfect results were acquired on functional evaluation and the mean Harris hip score was 90.7 (range: 83-95). The shaft angle of the neck was restored up to 5° and translation was decreased from 2.05 to 0.15 cm. In a study by Hoskins et al. (19), no major complications were observed in 20 patients who received cerclage application, whereas major complications were reported in 9.7% of a total of 135 patients; this rate increased to 11.4% in 20 patients when cerclage was not used. However, in this study, the mean union time was 20.16±2.8 (range: 16-28) weeks, mean LEFS score was 74.08±2.3 (range: 70-80), and LEFS percentage was 92.75±16.20 (range: 88-100). According to the radiological reduction quality evaluation criteria of Baumgaertner et al. (22,23), good results were acquired in 28 (84.8%) patients and acceptable results were obtained in 5 (15.2%) patients. The mean VAS score was 0.84±1.17 (range: 0-4). There were no major complications, apart from the delayed union observed in one patient (3%). There were minor complications in three (9%) patients, of which two had superficial infection, which was treated with antibiotic therapy, and one patient had a serous discharge. There were no patients who developed implant failure and there was no reduction loss that required reoperation.

Study Limitations

There are certain limitations in this study. Some parameters could not be retrospectively evaluated. There was no comparison group. Furthermore, the number of patients was relatively low and the

fracture types were classified according to the closest fracture type due to the absence of an optimal fracture classification system. There is need for prospective, randomized, controlled, and multicentric studies with comparisons in homogenous age groups and same fracture patterns with different fixation materials.

CONCLUSION

Spiral/oblique subtrochanteric femur fractures are difficult to treat due to the anatomical position and functional characteristics; therefore, complications are frequently observed. In addition, exposure to fluoroscopy during the surgery is an important disadvantage in the treatment. Treatment with long PFNA and cerclage cable application is a safe method that increases the stability of the fixation, allows early mobilization and weight bearing, and achieves good radiological and functional outcomes.

Ethics

Ethics Committee Approval: Approval for the study was granted by University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital Ethics Committee (approval no: 37732058-514.10).

Informed Consent: The study was conducted at our hospital and informed consent was preoperatively obtained from all the study patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.K., M.T., A.A., R.D., Concept: A.K., A.A., M.Ç.E., Design: A.K., A.A., M.T., M.Ç.E., Data Collection or Processing: E.Ö., M.İ., M.S.A., Analysis or Interpretation: E.Ö., M.İ., M.S.A., Literature Search: M.Ç.E., M.T., A.K., S.A., Writing: A.K., M.T.

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REFERENCES

1. Robinson CM, Houshian S, Khan LA. Trochanteric-entry long cephalomedullary nailing of subtrochanteric fractures caused by low-energy trauma. J Bone Joint Surg Am 2005;87:2217-26.
2. Tomás J, Teixidor J, Batalla L, Pacha D, Cortina J. Subtrochanteric fractures: treatment with cerclage wire and long intramedullary nail. J Orthop Trauma 2013;27:e157-60.
3. Codesido P, Mejía A, Riego J, Ojeda-Thies C. Subtrochanteric fractures in elderly people treated with intramedullary fixation: quality of life and complications following open reduction and cerclage wiring versus closed reduction. Arch Orthop Trauma Surg 2017;137:1077-85.
4. Bergman GD, Winquist RA, Mayo KA, Hansen ST Jr. Subtrochanteric fracture of the femur. Fixation using the Zickel nail. J Bone Joint Surg Am 1987;69:1032-40. Erratum in: J Bone Joint Surg [Am] 1988;70:152.
5. Kennedy MT, Mitra A, Hierlihy TG, Harty JA, Reidy D, Dolan M. Subtrochanteric hip fractures treated with cerclage cables and long cephalomedullary nails: a review of 17 consecutive cases over 2 years. Injury 2011;42:1317-21.
6. Lundy DW. Subtrochanteric femoral fractures. J Am Acad Orthop Surg 2007;15:663-71.
7. Bedi A, Toan Le T. Subtrochanteric femur fractures. Orthop Clin North Am 2004;35:473-83.
8. Apivatthakakul T, Phaliphot J, Leuvitoonvechkit S. Percutaneous cerclage wiring, does it disrupt femoral blood supply? A cadaveric injection study. Injury 2013;44:168-74.
9. Afsari A, Liporace F, Lindvall E, Infante A Jr, Sagi HC, Haidukewych GJ. Clamp-assisted reduction of high subtrochanteric fractures of the femur. J Bone Joint Surg 2009;91:1913-8.
10. Shukla S, Johnston P, Ahmad MA, Wynn-Jones H, Patel AD, Walton NP. Outcome of traumatic subtrochanteric femoral fractures fixed using cephalo-medullary nails. Injury 2007;38:1286-93.
11. Müller T, Topp T, Kühne CA, Gebhart G, Ruchholtz S, Zettl R. The benefit of wire cerclage stabilisation of the medial hinge in intramedullary nailing for the treatment of subtrochanteric femoral fractures: a biomechanical study. Int Orthop 2011;35:1237-43.
12. Barquet A, Mayora G, Fregeiro J, López L, Rienzi D, Francescoli L. The treatment of subtrochanteric nonunions with the long gamma nail: twenty-six patients with a minimum 2-year follow-up. J Orthop Trauma 2004;18:346-53.
13. Ban I, Birkelund L, Palm H, Brix M, Troelsen A. Circumferential wires as a supplement to intramedullary nailing in unstable trochanteric hip fractures: 4 reoperations in 60 patients followed for 1 year. Acta Orthop 2012;83:240-3.
14. Perren SM, Fernandez Dell'Oca A, Lenz M, Windolf M. Cerclage, evolution and potential of a Cinderella technology. An overview with reference to periprosthetic fractures. Acta Chir Orthop Traumatol Cech 2011;78:190-9.
15. Miedel R, Törnkvist H, Ponzer S, Söderqvist A, Tidermark J. Musculoskeletal function and quality of life in elderly patients after a subtrochanteric femoral fracture treated with a cephalomedullary nail. J Orthop Trauma 2011;25:208-13.
16. Pazzaglia UE, Congiu T, Raspanti M, Ranchetti F, Quacci D. Anatomy of the intracortical canal system: scanning electron microscopy study in rabbit femur. Clin Orthop Relat Res 2009;467:2446-56.
17. Mehta V, Finn HA. Femoral artery and vein injury after cerclage wiring of the femur: a case report. J Arthroplasty 2005;20:811-4.
18. Aleto T, Ritter MA, Berend ME. Case report: superficial femoral artery injury resulting from cerclage wiring during revision THA. Clin Orthop Relat Res 2008;466:749-53.
19. Hoskins W, Bingham R, Joseph S, Liew D, Love D, Bucknill A, et al. Subtrochanteric fracture: the effect of cerclage wire on fracture reduction and outcome. Injury 2015;46:1992-5.
20. Codesido P, Mejía A, Riego J, Ojeda-Thies C. Cerclage Wiring Through a Mini-Open Approach to Assist Reduction of Subtrochanteric Fractures Treated With Cephalomedullary Fixation: Surgical Technique. J Orthop Trauma 2017;31:e263-e8.

21. Marsh JL, Slongo TF, Agel J, Broderick JS, Creevey W, DeCoster TA, et al. Fracture and dislocation classification compendium - 2007: Orthopaedic Trauma Association classification, database and outcomes committee. J Orthop Trauma 2007;21(10 Suppl):S1-133.

22. Baumgaertner MR, Curtin SL, Lindskog DM. Intramedullary versus extramedullary fixation for the treatment of intertrochanteric hip fractures. Clin Orthop Relat Res 1998;87-94.

23. Baumgaertner MR, Curtin SL, Lindskog DM, Keggi JM. The value of the tip-apex distance in predicting failure of fixation of peritrochanteric fractures of the hip. J Bone Joint Surg Am 1995;77:1058-64.

24. Binkley JM, Stratford PW, Lott SA, Riddle DL. The Lower Extremity Functional Scale (LEFS): scale development, measurement properties, and clinical application. North American Orthopaedic Rehabilitation Research Network. Phys Ther 1999;79:371-83.

25. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med 1988;18:1007-19.

26. Gong JP, Yang Y, Liu PC, Nie XY, Li RL, Wu JZ, et al. PFNA with reduction assisted with pointed clamp and cable cerclagefor select subtrochanteric fractures of the femur. Int J Clin Exp Med 2016;9:2961-8.

27. Glassner PJ, Tejwani NC. Failure of proximal femoral locking compression plate: a case series. J Orthop Trauma 2011;25:76-83.

28. Kim JW, Park KC, Oh JK, Oh CW, Yoon YC, Chang HW. Percutaneous cerclage wiring followed by intramedullary nailing for subtrochanteric femoral fractures: a technical note with clinical results. Arch Orthop Trauma Surg 2014;134:1227-35.

29. MB. The blood supply of bone: an approach to bone biology. Butterworth-Heinemann 1971.

30. Steinberg EL, Shavit R. Braided cerclage wires: a biomechanical study. Injury 2011;42:347-51.

31. Apivatthakakul T, Siripipattanamongkol P, Oh CW, Sananpanich K, Phornphutkul C. Safe zones and a technical guide for cerclage wiring of the femur: a computed topographic angiogram (CTA) study. Arch Orthop Trauma Surg 2018;138:43-50.

32. Adanır O, Albay C, Beytemür O. Relationship Between Mortality and Timing of Surgery in Elderly Intertrochanteric Hip Fractures. Eur Arc Med Res 2017;33:23-7.

ORIGINAL ARTICLE

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Outcomes of Fixation of Slipped Capital Femoral Epiphysis with Single Cannulated Screw

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Abstract

Objective: Slipped capital femoral epiphysis (SCFE) or epiphysiolysis is a common pathology that requires urgent surgical intervention. This study aims at evaluating clinical and radiological mid-term results of our patients diagnosed with SCFE and fixed with a single cannulated screw.

Methods: We examined 13 hips of 12 patients treated with SCFE and evaluated mid-term results in our study.

Results: All of our patients were male with a mean age of 11.8 years (range 7-15). The mean slip angle was calculated as 43.20 degrees (range 26-70), and the average length of follow-up was 19 months (range 14-29 months). The average body mass index was 26.8 (range 24.4-29.7), and 11 patients were overweight (91.7%). Concerning ambulation, 7 patients had stable SCFE (58.3%), and 5 had unstable SCFE (41.6%). According to the Southwick classification, the average sliding angle of the patients was 43.2 degrees (range 26-70). Fixation was performed with a single cannulated screw for all patients. No patients were applied screws to the opposite hip for prophylactic purposes. Loss of reduction was not observed in any of our patients who followed up on average for 19 months (range 14 to 29). In radiological follow-ups, SCFE was not observed in the opposite hip of any patient. The postoperative range of motion was normal in all patients. Shortness and limping were not observed in any case.

Conclusion: We suggest that in SCFE cases requiring urgent surgery, the mild reduction can be considered, and subsequent osteosynthesis with a single screw is a sufficient treatment.

Keywords: Slipped capital femoral epiphysis, hip disorders, pediatric, adolescent, hip

INTRODUCTION

Slipped capital femoral epiphysis (SCFE) or epiphysiolysis is a common disease seen in pediatric patients, where the femoral head growth plate displaced inferiorly and posteriorly according to the length and is most common in the age range of 10-16 years (1,2). Its incidence is around 3-10/100,000 (3). The boy/girl ratio is about 1.4 and is more common in the black race (4). The etiology and treatment of SCFE remain controversial. They can be caused by various factors such as stress on the growth plate due to obesity, endocrine disorders (hypothyroidism, panhypopituitarism, and renal osteodystrophy), and the period of a rapid growth spurt during adolescence (5).

A characteristic patient presents with an antalgic gait and externally rotated limb with possible shortening, non-specific thigh-, groin-, or referred knee pain, and altered abductor function with exercise-triggered weakness of the lower extremity (5). There are delays in diagnosis in patients whose hip complaints are not at the forefront. In physical examination, decreased hip movements and minimal internal rotation should suggest SCFE in the differential diagnosis. Diagnosis of the disease can be made by hip anterior-posterior (AP) and lateral radiographs. Early diagnosis and appropriate treatment can reduce the morbidity and complications of SCFE, including arthrosis, loss of motion, and pain (6).

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After diagnosis, surgical stabilization is indicated in which the surgical options are determined by the severity of the slip, the presumed duration of the disease (acute or chronic), and the expertise of the treating surgeon. Various treatment options have been proposed, including bone peg epiphysiodesis, pinning *in situ* closed reduction and pinning, open reduction and physeal osteotomy, open reduction and internal fixation, and Ganz surgical dislocation. However, the surgical procedure involving the placement of one screw across the growth plate is technically straightforward, considered minimally invasive, and continues to be widely used (3,7). Complications such as femoral head avascular necrosis, chondrolysis, nerve injury, implant failure, infection, subtrochanteric fracture, and continued slippage can be seen after surgical treatment (3,7,8).

Our study aimed to evaluate clinical and radiological mid-term results of the sliding femoral head epiphysis after mild reduction with a single screw or fixation in the position where it is located.

METHODS

The study was conducted following the ethical standards stated in the "Declaration of Helsinki" and was approved by the Local Ethics Committee of Fatih Sultan Mehmet Training and Research Hospital (number: 17073117-050.06). Informed consent was obtained from all patients.

A total of 12 patients were admitted to our emergency department or orthopedics outpatient clinic with complaints of hip, knee, thigh pain, and limping, and diagnosed with SCFE after the physical examination and X-ray graphs were included in the study (Figure 1). Internal fixation was performed on 13 hips of 12 patients, including 6 in its position and 7 after mild reduction with a single cannulated screw. All of the patients were male. Five of our patients were examined as acute and two as chronic sliding. No patient underwent surgery on the prophylactic contralateral hip. The degrees of sliding was determined on the lateral graphy using the Southwick classification (9). According to this classification, those with a sliding below 30 degrees were classified as mild, those with sliding between 30 and 60 degrees were classified as moderate, and those with a sliding higher than 60 degrees were classified as severe (Table 1). SCFE cases were classified as stable and unstable according to the way patients were referred to the emergency department, and the stability was confirmed by intra-operative scopy. Heyman-Herndon classification was used in the clinical examination of our cases (Table 2) (10).

All patients were operated on the traction table under general anesthesia. A mini-incision was entered lateral to the hip, where the screw will be applied. A 6.5 mm titanium spongious cannulated screw (TST, Istanbul, Turkey) was applied percutaneously under fluoroscopy control. The K-wire guided from the anterior of the basis of the femoral neck sent extracapsular toward the posteromedial, centralizing the femoral neck (Figure 2). Reduction and screw length was controlled by scopy. The opposite hips were also evaluated with movable scopy images, and no unstable epiphysis was observed except for the bilateral patient. Screw application to the opposite hip was performed only in one patient with a diagnosis of bilateral SCFE. The patients were mobilized with double crutches on the postoperative first day without loading the operative side. The patients were mobilized with a partial load from the sixth postoperative week. In the only patient with bilateral sliding, only in-bed movements were allowed for 6 weeks. All of the patients were discharged on the second postoperative day.

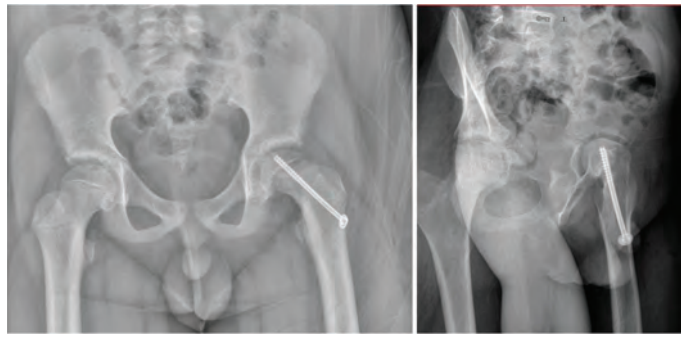

Figure 1. On the AP and lateral radiographs of our 10-year-old patient who applied to our emergency department with hip and thigh pain, the femoral head epiphysis is seen to have slid posteriorly and inferiorly
AP: Anterior-posterior

Table 1. Age, gender, side, degree of shifting, and body mass index values of the patients before surgery

Patient	Age	Gender	Slip angle (degrees)	BMI
1	10	M	70	26.1
2	7	M	35 (R) and 40 (L)	29.7
3	12	M	62	25.9
4	10	M	26	26.5
5	11	M	35	26.8
6	12	M	40	28.2
7	15	M	32	25.5
8	12	M	42	27.1
9	13	M	39	29.2
10	14	M	51	26.3
11	13	M	44	24.4
12	13	M	36	26.2

R: Right, L: Left, M: Male, BMI: Body mass index

Table 2. Heyman-Herndon SCFE clinical examination classification							
Group	**Rating**	**Limp**	**Pain**	**Internal rotation**	**Flexion**	**Abduction**	**Reconstructive surgery**
1	Excellent	No	No	Normal	Normal	Normal	No
2	Good	No	No	Slight limitation	normal	Normal	No
3	Fair	No	No	Slight limitation	Normal	Slight limitation	No
4	Poor	Mild	Slight after strenuous activity	Slight limitation	Slight limitation	Slight limitation	No
5	Failure	Yes	With activity	Marked limitation	Marked limitation	Marked limitation	Yes
SCFE: Slipped capital femoral epiphysis							

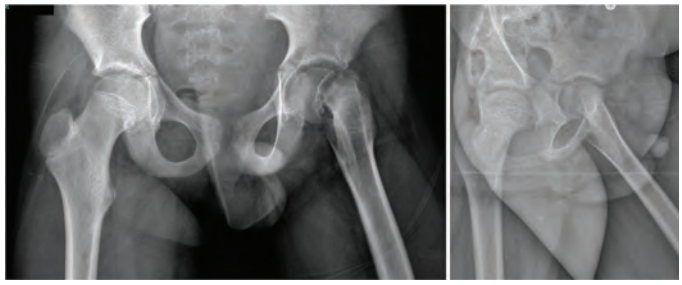

Figure 2. Our patient underwent osteosynthesis with a cannulated screw under emergency conditions

Statistical Analysis

The statistical analyses were performed using SPSS, version 22 (IBM SPSS Statistics for Windows, Armonk, NY; IBM Corp., Released 2013). No sample size estimations were performed because all patients in our hospital database who met the inclusion criteria were analyzed. Therefore, the statistical significance level was set to $p<0.05$.

RESULTS

Thirteen hips of 12 patients were evaluated clinically and radiologically. The age of the patients ranged from 7 to 15 years, and the mean age of patients who underwent surgery was 11.8 years. The average length of follow-up was 19 months (range 14-29 months). The average body mass index (BMI) was 26.8 (range 24.4-29.7), and 11 patients were overweight (91.7%) (Table 1). With regard to ambulation, 7 patients had stable SCFE (58.3%), and 5 had unstable SCFE (41.6%). With respect to symptoms, there were 9 patients with acute SCFE (75%), 2 patients with chronic SCFE (16.7%), and 1 with acute episodes in the chronic phase (8.3%). According to the Southwick classification, the average sliding degrees of the patients were 43.2 (range 26-70). In order to investigate the severity of displacement, we measured one hip with mild displacement, 9 hips with moderate displacement, and two hips with severe displacement. The postoperative range of motion was normal in all patients. Shortness and limping were not observed in any case. Subchondral cyst, osteophytic formation, and subchondral sclerosis were not observed in comparative radiographs of the patients. No degenerative changes were detected in any of our patients according to Boyer's criteria.

DISCUSSION

There are a limited number of studies on SCFE in our country. Our study retrospectively discussed the results of our patients diagnosed with acute and chronic SCFE and operated with a percutaneous single cannulated screw application. Despite the low number of patients, we found that our mid-term results correlated with the literature after single cannulated screw fixation.

SCFE femoral head is a condition in which the pineal plate changes inferiorly and posteriorly compared to its length. As a result, flexion, abduction, and internal rotation movements in the hip are restricted, and when the hip is intended to be flexed, it is directed toward external rotation (7).

SCFE is a disease most common in the 10-16 age range. The mean age of our patients was 11.8 (7-13). While the male/female ratio was 1.4/1 in the literature, our entire patient group was males (4). Bilateral involvement in SCFE is around 20-25% (11,12). In our patient group, only one patient had bilateral SCFE, and its ratio to the patient group was 8.3%.

Although the SCFE etiology is not fully known, environmental and genetic causes are emphasized. Endocrine causes such as hypogonadism, hypothyroidism, hypopituitarism, mechanical factors such as obesity and trauma, inflammatory diseases, and chronic kidney failure can be included in the etiology of the disease (2,5). Especially in cases under 10 and over 16, endocrine causes must be investigated. In our patient group, the mean BMI was 26.8 (24.4-29.7) and was above average compared with the age, except for one patient. One of our patients who was evaluated as chronic SCFE was 7 years old with a BMI of 29.7. This patient

was diagnosed with hypogonadism as a result of a pediatric endocrinology consultation.

The options for SCFE surgical treatment include *in situ* nailing for mild shifts, bone nails for moderate to severe shifts, and a combination of epiphysiodes and osteotomy or nailing and osteotomy according to the severity and level of the shift (3,7,13). In recent years, the popular surgical method is single screw fixation (7,8,14,15). However, Southwick osteotomy is recommended as a technically challenging but safe procedure, especially in treating chronic, stable, and moderate SCFE. It is stated that it corrects the deformity in the hip and provides a functional hip (16). However, we preferred the fixation method with one screw in three cases that we considered chronic. Some researchers suggest *in situ* nailings in moderate shifts, whereas others suggest epiphysiodes with bone nails (17-20). The increase in the number and size of implants used in surgical treatment also increases the complication rate. Accordingly, there is an increase in complications such as femoral head avascular necrosis, chondrolysis, penetration of the nail into the joint, and infection (7,21-23). Our shortest follow-up period was 14 months, and chondrolysis and avascular necrosis, which were shown to develop especially in the first year, were not observed in our follow-ups.

The prophylactic nailing of the opposite hip is still controversial in patients with unilateral involvement. Greenough et al. (24) observed that the complication rate increased in their series; therefore, they did not recommend prophylactic nailing. On the other hand, some authors suggest that the opposite hip should be preserved in patients who develop SCFE due to the high probability of bilateral disease (25,26). We did not perform preventive surgery on any of our patients, and no slipped epiphysis was observed in the opposite hip of any of our patients.

For fixation in its location, it is necessary to provide a good AP and lateral vision with the help of a scopy on the traction table. In order to detect femoral head epiphysis in increasing slip degrees, the entry point of the nail is displaced toward the anterior cortex of the femoral neck (14). For all the patients in our study group, full AP and lateral images were taken on the traction table accompanied by scopy on the traction table, and nailing was performed with anterolateral entry. It has been reported in various studies that reduction maneuver causes poor results and that the risk of chondrolysis and avascular necrosis increases (15,27). Six of our patients underwent mild reduction maneuvers, and none of the complications stated were observed in the follow-up of these patients.

A study conducted showed that the complication rate increased parallel with the increasing sliding degrees (15). The average sliding rate in our cases was 42.8. Therefore, we consider that not too high sliding degrees in our cases are another reason for no complications. Our follow-ups observed that hip flexion, internal rotation, and abduction, which were restricted preoperatively, improved, and excellent results were obtained in all of our patients.

Study Limitations

Our study has some limitations. The first limitation is that the same physician performed the radiological evaluation. Second, we did not have a large patient series and reported only mid-term results.

CONCLUSION

We suggest that in SCFE cases requiring urgent surgery, the mild reduction can be considered, and subsequent osteosynthesis with a single screw is a sufficient treatment.

Ethics

Ethics Committee Approval: The study was conducted following the ethical standards stated in the "Declaration of Helsinki" and was approved by the Local Ethics Committee of Fatih Sultan Mehmet Training and Research Hospital (number: 17073117-050.06).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.E., A.T.P., Concept: T.E., Design: A.T.P., Data Collection or Processing: A.T.P., Analysis or Interpretation: T.E., Literature Search: A.T.P., Writing: T.E.

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REFERENCES

1. Lehmann CL, Arons RR, Loder RT, Vitale MG. The epidemiology of slipped capital femoral epiphysis: an update. J Pediatr Orthop 2006;26:286-90.
2. Georgiadis AG, Zaltz I. Slipped capital femoral epiphysis: How to evaluate with a review and update of treatment. Pediatr Clin North Am 2014;61:1119-35.
3. Naseem H, Chatterji S, Tsang K, Hakimi M, Chytas A, Alshryda S. Treatment of stable slipped capital femoral epiphysis: Systematic

review and exploratory patient level analysis. J Orthop Traumatol 2017;18:379-94.

4. Loder RT. The demographics of slipped capital femoral epiphysis. An international multicenter study. Clin Orthop Relat Res 1996;8-27.
5. Gholve PA, Cameron DB, Millis MB. Slipped capital femoral epiphysis update. Curr Opin Pediatr 2009;21:39-45.
6. Hägglund G, Hannson LI, Sandström S. Slipped capital femoral epiphysis in southern Sweden. Long-term results after nailing/pinning. Clin Orthop Relat Res 1987;190-200.
7. Bittersohl B, Hosalkar HS, Zilkens C, Krauspe R. Current concepts in management of slipped capital femoral epiphysis. Hip Int 2015;25:104-14.
8. Boyer DW, Mickelson MR, Ponseti IV. Slipped capital femoral epiphysis. Long-term follow-up study of one hundred and twenty-one patients. J Bone Joint Surg Am 1981;63:85-95.
9. Southwick WO. Osteotomy through the lesser trochanter for slipped capital femoral epiphysis. J Bone Joint Surg Am 1967;49:807-35.
10. Zahrawi FB, Stephens TL, Spencer GE Jr, Clough JM. Comparative study of pinning in situ and open epiphysiodesis in 105 patients with slipped capital femoral epiphyses. Clin Orthop Relat Res 1983;160-8.
11. Loder RT, Starnes T, Dikos G. Atypical and typical (idiopathic) slipped capital femoral epiphysis. Reconfirmation of the age-weight test and description of the height and age-height tests. J Bone Joint Surg Am 2006;88:1574-81.
12. Burrow SR, Alman B, Wright JG. Short stature as a screening test for endocrinopathy in slipped capital femoral epiphysis. J Bone Joint Surg Br 2001;83:263-8.
13. Slongo T, Kakaty D, Krause F, Ziebarth K. Treatment of slipped capital femoral epiphysis with a modified Dunn procedure. J Bone Joint Surg Am 2010;92:2898-908.
14. Aronson DD, Carlson WE. Slipped capital femoral epiphysis. A prospective study of fixation with a single screw. J Bone Joint Surg Am 1992;74:810-9.
15. Boero S, Brunenghi GM, Carbone M, Stella G, Calevo MG. Pinning in slipped capital femoral epiphysis: Long-term follow-up study. J Pediatr Orthop B 2003;12:372-9.
16. Coppola C, Sadile F, Lotito FM, Cigala F, Shanmugam C, Maffulli N. Stabil femur başi epifiz kaymasinda Southwick osteotomisi: Uzun dönem sonuçlar [Southwick osteotomy in stable slipped capital femoral epiphysis: a long-term outcome study]. Acta Orthop Traumatol Turc 2008;42:358-64.
17. Cullu E, Damgaci K, Savk SO. Femur başi epifiz kaymasinda olduğu pozisyonda tek vida ile tespit [In situ pinning on slipped femoral capital epiphysis with a single cannulated screw]. Ulus Travma Acil Cerrahi Derg 2005;11:212-7.
18. Sibiński M, Synder M, Borowski A, Grzegorzewski A. Przebudowa blizszego końca kości udowej po szyjkowo-glowowej transfiksji in situ w młodzieńczym złuszczeniu [Remodeling after in situ pinning for slipped capital femoral epiphysis]. Chir Narzadow Ruchu Ortop Pol 2004;69:321-4.
19. Adamczyk MJ, Weiner DS, Hawk D. A 50-year experience with bone graft epiphysiodesis in the treatment of slipped capital femoral epiphysis. J Pediatr Orthop 2003;23:578-83.
20. Schmidt TL, Cimino WG, Seidel FG. Allograft epiphysiodesis for slipped capital femoral epiphysis. Clin Orthop Relat Res 1996;61-76.
21. Seller K, Raab P, Wild A, Krauspe R. Risk-benefit analysis of prophylactic pinning in slipped capital femoral epiphysis. J Pediatr Orthop B 2001;10:192-6.
22. Loder RT, Richards BS, Shapiro PS, Reznick LR, Aronson DD. Acute slipped capital femoral epiphysis: the importance of physeal stability. J Bone Joint Surg Am 1993;75:1134-40.
23. Tudisco C, Caterini R, Farsetti P, Potenza V. Chondrolysis of the hip complicating slipped capital femoral epiphysis: long-term follow-up of nine patients. J Pediatr Orthop B 1999;8:107-11.
24. Greenough CG, Bromage JD, Jackson AM. Pinning of the slipped upper femoral epiphysis--a trouble-free procedure? J Pediatr Orthop 1985;5:657-60.
25. Hägglund G. The contralateral hip in slipped capital femoral epiphysis. J Pediatr Orthop B 1996;5:158-61.
26. Loder RT, Hensinger RN. Slipped capital femoral epiphysis associated with renal failure osteodystrophy. J Pediatr Orthop 1997;17:205-11.
27. Stevens DB, Short BA, Burch JM. In situ fixation of the slipped capital femoral epiphysis with a single screw. J Pediatr Orthop B 1996;5:85-9.

ORIGINAL ARTICLE

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Our Hybrid Approach in the Treatment of Peripheral Vascular Diseases

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Abstract

Objective: Peripheral arterial disease is a critical health problem with an incidence of approximately 13% in the population over 50 years of age. Although endovascular interventions provide successful results as sole treatment in many patients, concomitant surgical interventions may be necessary to provide complete revascularization of the target extremities in complex peripheral vascular disease cases. In this study, we aimed to present the early results of 21 patients who underwent hybrid peripheral vascular intervention

Methods: Twenty one patients who underwent hybrid procedures for peripheral arterial disease between January 2018 and June 2018 were included in the study. One of the patients underwent an open surgery primarily, and the endovascular intervention was applied after 1 month of surgery. Endovascular and surgical procedures were performed simultaneously in all other patients.

Results: Fifteen patients were male (71.4%), and 6 were female (28.6%). The mean age of patients was 61.95±7.88 [mean ± standard deviation/standard error of mean (SD/SEM)] years, with an age range of 52-75 years. The average ankle-brachial index of the targeted extremity was 0.25±0.12 (mean ± SD/SEM).

Conclusion: The hybrid procedures provided the best benefit possible for the complex arterial lesions with increased inflow and distal flow.

Keywords: Hybrid method, peripheral vascular diseases, endovascular treatment

INTRODUCTION

Peripheral arterial disease is an important health problem with an incidence of approximately 13% in the population over 50 years of age (1). Although there are many etiological factors, atherosclerosis is the most common cause (2). Because of the systemic nature of atherosclerosis, 60% of these patients have simultaneous coronary artery disease, and 30% have cerebrovascular pathologies (3). 10-15% of the patients with intermittent claudication die of cardiovascular diseases within 5 years. Although many patients may be asymptomatic, the indication of the intervention and the clinical classification are determined according to the severity of the symptoms. Claudication is the main reason for intervention in most patients, and the type of intervention depends on the severity of the disease.

In the last two decades, due to the rapidly improving endovascular intervention methods and increasing experience in this field, catheter-based procedures have become the first line of treatment in peripheral artery disease (PAD). Therefore, this approach is considered the "Endo-first" approach. Although endovascular interventions provide successful results as sole treatment in many patients, concomitant surgical interventions may be necessary to provide complete revascularization of the target extremities in complex peripheral vascular disease cases. Although hybrid operating room settings provide ideal conditions, the C-arm scope device in standard operating rooms can be sufficient in many cases. This study aimed to present the early results of 21 patients who underwent hybrid peripheral vascular surgery with the help of a C-arm scope device under standard operating room conditions between January-June 2018 in our clinic.

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METHODS

Patient Selection

In this study, data from the clinical database were analyzed retrospectively. The patients admitted to the cardiovascular surgery clinic and diagnosed with PAD and then underwent hybrid intervention were analyzed.

The ankle-brachial index (ABI) of all patients was measured after a detailed history and physical examination. In patients with ABI <0.9, computed tomographic (CT) angiography was performed. In addition, all patients underwent carotid doppler and cardiac examination, except for two patients who were operated on under emergency conditions. Patients were classified by using Fontaine classification, and patients with Fontaine 2B or higher with comorbidities were considered and treated with hybrid therapy. All patients participating in the study were informed about the study, and their consent was obtained. Ethics Committee Okmeydanı Training and Research Hospital approved this study (approval number: 48670771-514.10, date: 14.05.2019).

Surgical Technique

Operations were performed under either general anesthesia, local anesthesia, or peripheral nerve block. Long superficial femoral artery (SFA) occlusions (>25 cm) were treated with prosthetic bypass grafting in elective conditions. Endarterectomy was performed for the lesions, which may cause anatomic and physiological stenosis in the main femoral artery or to relieve stenoses limiting the inflow. In addition, simultaneous profundoplasty was performed in the presence of osteal stenosis of the deep femoral artery.

Endovascular treatment methods were applied to patients with aorta-iliac lesions shorter than 5 cm, SFA lesions shorter than 25 cm, or distal arterial lesions. Endovascular techniques used were atherectomy, percutaneous balloon angioplasty, and/or drug-coated percutaneous balloon angioplasty. In addition, since most patients had simultaneous endovascular and surgical procedures, catheterization was performed from the explored artery for endovascular treatment.

Statistical Analysis

Statistical analyzes were performed using SPSS (SPSS Inc., Chicago, IL, USA) version 16.0. Continuous variables are presented as mean ± standard deviation and categorical variables as n and percentage values.

RESULTS

The study included a total of 21 patients who underwent hybrid procedures for peripheral arterial disease between January 2018 and June 2018. 15 of the patients were male (71.4%), and 6 were female (28.6%). The mean age of patients was 61.95±7.88 years, with an age range of 52-75 years. The most common risk factor was smoking (80.9%). The other risk factors related to the patients were summarized in Table 1. Two patients (9.5%) had ischemic wounds (Fontaine class 4), 14 patients (66.6%) had claudication (Fontaine class 2B), and 5 patients (23.9%) had rest pain (Fontaine class 3). The average ABI in the targeted extremity was 0.25±0.12.

Interventions were performed in 18 patients under general anesthesia, 2 patients under local anesthesia, and one patient with a peripheral nerve block. Femoro-popliteal bypass was performed in 10 patients due to long-segment superficial femoral artery lesions (>25 cm). Six patients underwent endarterectomy to the main femoral artery. Extra anatomic femoro-femoral bypass was performed in 2 patients. Interposition with autogenous vein, bilateral embolectomy, and extra anatomic axillo-femoral bypass was performed in each one patient. In the same session, 6 patients underwent self-expandable main iliac artery stent implantation, 11 patients underwent anterior tibial artery percutaneous transluminal balloon angioplasty, and 3 patients underwent superficial femoral artery percutaneous transluminal balloon angioplasty. Detailed data on patient procedures are summarized in Table 2.

For the patient who underwent femoro-femoral bypass and the deep femoral artery plasty, transposition from the superficial femoral artery to the deep femoral artery was performed percutaneous transluminal balloon angioplasty. An application of vacuum assisted closure for prolonged service hospitalization and wound infection was required in the inguinal incision in this patient. As a result, this patient increased the average length of

Table 1. Demographic data

Risk factor	Number (n)	Percentage (%)
Hypertension	9	42.8
Diabetes mellitus	13	61.9
Hyperlipidemia	6	28.5
Coronary artery disease	8	38
Smoking	17	80.9
Infrarenal abdominal aortic aneurysm	1	4.7
Carotid artery stenosis	1	4.7
Small cell lung cancer	1	4.7

Table 2. Surgical and endovenous procedures applied to the patients

Procedure	Number of patients
Right CFA endarterectomy + right CIA stent	3
Right femoropopliteal bypass + right ATA angioplasty	3
Left femoropopliteal bypass + left ATA angioplasty	4
Right CFA endarterectomy + right ATA angioplasty	2
Femoro-femoral bypass + left SFA angioplasty	2
Femoro-femoral bypass + right CIA stent	1
Right femoropopliteal bypass + right CIA stent	3
Left popliteal artery vein graft interposition + left ATA angioplasty	1
Left axillo-femoral bypass + left ATA angioplasty	1
Bilateral femoral embolectomy + right SFA angioplasty	1

ATA: Anterior tibial artery, SFA: Superficial femoral artery, CIA: Common iliac artery, CFA: Common femoral artery

stay. The mean length of hospitalization was 3.15±2.94 days. There was no acute renal failure or mortality in the postoperative period. Two patients with ischemic injuries were referred to hyperbaric oxygen therapy at the end of postoperative follow-up. One of the two patients underwent interposition surgery with an autogenous graft to the popliteal artery under emergency conditions, and the other patient underwent bilateral femoral artery embolectomy operation. One of the patients underwent at first endovascular intervention before one month to open surgery. This patient underwent endovascular intervention guided by arterial doppler ultrasonography of the main femoral artery. The mean of AAI was 0.83±0.15 in the postoperative follow-up period.

DISCUSSION

This retrospective study presents our experience in 21 patients who underwent a hybrid intervention. We performed simultaneous endovascular and surgical treatment in 20 patients and staged hybrid in one patient. The hybrid approach is defined as the combined utilization of open surgery and endovascular methods in the same case. PAD is a systemic disease. Ozkan et al. (4) reported their series of the 626 patients, 400 (64%) had multisegmental disease, the most common form of combined femoropopliteal and crural disease (25%). Neither open surgery nor endovascular approach could provide complete revascularization in some of these complex cases. The present study aimed to discuss the importance of the hybrid approach following current European Society for Vascular Surgery guidelines recommendations.

While the discussion on the choice of treatment continues, the latest published European Society of Cardiology guideline suggests endovascular treatment as the first choice for occlusive lesions shorter than 5 cm in terms of revascularization of aorta-iliac disease and aorta-bifemoral bypass class I defined as indicated for aorta-iliac occlusions without serious comorbidity. Furthermore, in patients with long and/or bilateral aorta-iliac occlusive lesions with severe comorbidity, the need for endovascular intervention was emphasized as the first strategy with class I indication.

In the same guideline, endovascular treatment for occlusive femoropopliteal lesions below 25 cm and autologous vein grafting for lesions above 25 cm are presented as the first strategy with class I indication. Transluminal balloon angioplasty and stenting process of the aorta-iliac region has a high primary and secondary patency rate. Primary patency in short lesions (<5 cm) after transluminal angioplasty is reported as 64.5%, and secondary patency is found to be 81.8% (5).

The aortoiliac occlusive disease is generally associated with severe comorbidities. Aortobifemoral or aortobiiliac bypass is still the preferred approach in complex cases with 5 and 10 years patency rates of approximately 90% and 75%, respectively (6,7). Aortic bifurcated surgery is a high-risk procedure. Bredahl and colleagues reported 3.6% of cases showed 30-day mortality, and 20% of cases showed 30-day major complications in their 20 years of experience (8). In the last decade, Endovascular Aneurysm Repair, Covered Endovascular Repair of Aortic Bifurcation (CERAB), and the kissing stent technique have become a current first line treatment in experienced centers. The endovascular approach has comparable midterm results but has better early-term outcomes regarding mortality, hospital stays, bleeding, infection, and mesenteric ischemia. We also prefer both CERAB and the kissing stent technique in complex cases. We reported 7 patients underwent simultaneous uniiliac endovascular intervention and peripheric arterial surgery with 100% procedural success in this series. Primary iliac stenting was the preferred technique in each case. Peripheric surgery was planned considering both preoperative CT angiography and DSA during the iliac procedure.

Jorshery et al. (9) compared hybrid interventions with a peripheral bypass with saphenous vein and prosthetic graft in patients with complex pad. They reported that hybrid procedures have favorable perioperative outcomes compared with open bypass for femoropopliteal revascularization. Our

series combined femoropopliteal bypass and distal angioplasty in 7 cases, common femoral endarterectomy and angioplasty in 2 cases, and bilateral embolectomy and angioplasty in 1 case. Each case was discharged uneventfully with 100% early-term success (9).

CONCLUSION

In conclusion, the hybrid procedures provide the best benefit possible for the complex arterial lesions with the increase of both inflow and distal run-off. Hybrid procedures may also reduce hospital stay, mortality, and morbidity.

Ethics

Ethics Committee Approval: Ethics Committee Okmeydanı Training and Research Hospital approved this study (approval number: 48670771-514.10, date: 14.05.2019).

Informed Consent: All patients participating in the study were informed about the study, and their consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.Y., S.K., Concept: N.K., Design: N.K., Data Collection or Processing: C.Y., S.K., B.Ç.K., Analysis or Interpretation: M.G., Literature Search: M.G., B.Ç.K., Writing: C.Y.

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REFERENCES

1. Crawford F, Welch K, Andras A, Chappell FM. Ankle brachial index for the diagnosis of lower limb peripheral arterial disease. Cochrane Database Syst Rev 2016;9:CD010680.
2. Aronow WS. Management of peripheral arterial disease of the lower extremities in elderly patients. J Gerontol A Biol Sci Med Sci 2004;59:172-7.
3. Viles-Gonzalez JF, Fuster V, Badimon JJ. Atherothrombosis: a widespread disease with unpredictable and life-threatening consequences. Eur Heart J 2004;25:1197-207.
4. Ozkan U, Oguzkurt L, Tercan F. Atherosclerotic risk factors and segmental distribution in symptomatic peripheral artery disease. J Vasc Interv Radiol 2009;20:437-41.
5. Abello N, Kretz B, Picquet J, Magnan PE, Hassen-Khodja R, Chevalier J, et al. Long-term results of stenting of the aortic bifurcation. Ann Vasc Surg 2012;26:521-6.
6. Lun Y, Zhang J, Wu X, Gang Q, Shen S, Jiang H, et al. Comparison of midterm outcomes between surgical treatment and endovascular reconstruction for chronic infrarenal aortoiliac occlusion. J Vasc Interv Radiol 2015;26:196-204.
7. Grimme FA, Goverde PC, Verbruggen PJ, Zeebregts CJ, Reijnen MM. Editor's Choice--First Results of the Covered Endovascular Reconstruction of the Aortic Bifurcation (CERAB) Technique for Aortoiliac Occlusive Disease. Eur J Vasc Endovasc Surg 2015;50:638-47.
8. Bredahl K, Jensen LP, Schroeder TV, Sillesen H, Nielsen H, Eiberg JP. Mortality and complications after aortic bifurcated bypass procedures for chronic aortoiliac occlusive disease. J Vasc Surg 2015;62:75-82.
9. Jorshery SD, Skrip L, Sarac T, Ochoa Chaar CI. Hybrid femoropopliteal procedures are associated with improved perioperative outcomes compared with bypass. J Vasc Surg 2018;68:1447-54.

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Evaluation of Preoperative Carcinoembryonic Antigen Positivity in Relation to Volume-based PET/CT Parameters in Patients with Colorectal Cancer

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Abstract

Objective: This study aimed to determine the relationship between the tumor load and carcinoembryonic antigen (CEA) positivity by comparing CEA positivity and volume-based positron emission tomography/computed tomography (PET/CT) preoperative parameters in patients with colorectal cancer.

Methods: This retrospective study included a total of 87 patients with colorectal cancer who underwent PET/CT between January 2018 and December 2019 and had simultaneous CEA measurements. CEA level ≥5 ng/mL was accepted as positive. Patients who underwent surgery or received chemotherapy/radiotherapy were excluded from the study. The maximum standardized uptake value (SUV_{max}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) values were calculated using ^{18}fluoro-fluorodeoxyglucose PET/CT images of the patients.

Results: CEA was positive in 43 (49.4%) patients. The site of the primary lesion was the rectum in 40 (46%) patients, sigmoid colon in 19 (21.8%), ascending colon in 14 (16.1%), descending colon in 9 (10.3%), transverse colon in 3 (3.4%), hepatic flexure in 1 (1.1%), and descending-sigmoid colon junction in 1 (1.1%). No significant association was noted between the intestinal segment of the primary lesion and CEA positivity (p=0.878). Moreover, no significant difference was found among SUV_{max}, MTV, and TLG values of the primary tumor and CEA positivity (p=0.611, p=0.980, and p=0.527, respectively).

Conclusion: Preoperatively, no significant relationship was found between CEA positivity and volume-based PET/CT parameters, specifically MTV and TLG, in patients with colon cancer. CEA positivity in the preoperative period has low diagnostic effectiveness independent of the tumor load.

Keywords: FDG PET/CT, colorectal carcinoma, carcinoembryonic antigen, metabolic tumor volume, total lesion glycolysis

INTRODUCTION

Colorectal cancer is the third leading cancer type and one of the most common causes of cancer-related deaths (1). Colorectal cancers are diagnosed by colonoscopic and histopathological examination, and tumor markers are important for screening and detecting recurrences. Carcinoembryonic antigen (CEA) is one of the main tumor markers used in diagnosing colorectal cancers (2,3). CEA has a glycoprotein structure, and preoperative and postoperative measurements of its serum level have been considered clinically useful (4).

^{18}fluoro-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is a frequently used imaging method for metabolic characterization, staging, treatment response evaluation, radiotherapy planning, and restaging of colorectal cancers (5). The maximum standardized uptake value (SUV_{max}) measured with ^{18}F-FDG PET/CT is a preoperative prognostic factor for patients with colorectal cancer (6). Recently, some volume-based metabolic parameters such as the metabolic active tumor volume (MTV) and total lesion glycolysis (TLG) have also been studied as prognostic factors (7,8).

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To our knowledge, only a limited number of studies have investigated the relationship between serum CEA levels and volume-based PET/CT parameters in patients with colorectal cancer, and most of these studies focused on recurrence assessment (9,10). Thus, in the present study, we aimed to determine the relationship between the tumor load and CEA positivity by comparing preoperative period CEA positivity and volume-based PET/CT parameters in patients with colorectal cancer.

METHODS

This retrospective study included 87 patients with colorectal cancer who underwent PET/CT and had simultaneous CEA measurements between January 2018 and December 2019 at the department of nuclear medicine in Gazi Yasargil Training and Research Hospital. Overall, 23 patients were female and 64 were male, and their mean age was 56.7±15.44 years. Patients with an interval of more than 1 week between CEA measurement and ^{18}F-FDG PET/CT and patients with distant organ and lymph node metastases found in PET/CT were excluded from the study. Patients with M0 and N0 status were included in the study. Participant selection was performed during the preoperative period. Furthermore, patients who received chemotherapy/radiotherapy were excluded. All patients who met the inclusion criteria were consecutively included in the study. SUV_{max}, MTV, and TLG values were calculated by using the ^{18}F-FDG PET/CT images of these patients. Collected data and CEA results were compared statistically.

This study was conducted in accordance with the local good clinical practice guidelines and current legislations. Permission was obtained from the Institutional Ethics Committee of the University Health Science Turkey of Gazi Yasargil Training and Research Hospital for the use and publication of patient data (protocol no: 435/2020).

^{18}F-FDG PET/CT Imaging Protocol

All patients were instructed not to eat at least 6 h before the intervention, and intravenous administration of glucose was stopped. Before the injection of ^{18}F-FDG, blood glucose values were confirmed to be ≤140 mg/dL by finger stick measurement method. Moreover, 60 min after the injection of 3.5-5.5 MBq/kg ^{18}F-FDG, CT was performed from the supine position using the Discovery IQ 4 ring 20 cm axial field of view (FOV) PET/CT scanner (GE Healthcare, Milwaukee, WI, USA) in the supine position, from the vertex to the middle of the thigh. The scanning parameters were as follows: Tube voltage, 120 kV; tube current, 80 mAs/slice; FOV, 700 mm, transaxial without gap; collimation, 64×0.625 mm; pitch, 1.4; rotation time, 0.5 s; slice thickness, 3.3 mm; matrix size, 512×512. Then, 2.5 min bedside PET images were obtained at three-dimensional FOV of 20 cm, ordered subset expectation-maximization algorithm of 5 iterations/12 subsets, and full width at half maximum of 3 mm.

Analysis of Images

All ^{18}F-FDG PET/CT images were evaluated using PET volume computerized assisted reporting software (GE Advantage Workstation software version AW 4.7, USA) by two nuclear medicine specialists with at least 10 years of experience. The volumetric region of interest was drawn manually from the primary lesion in the colon or rectum in three planes, and the lesion and automatic MTV, TLG (MTV × SUV_{mean}), and SUV_{max} values were obtained by the device for each lesion using 40% SUV threshold (Figure 1).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, NY). The normality of continuous variables was evaluated by the Shapiro-Wilk-Francia test, and variance homogeneity was evaluated by Levene test. For the comparison of two independent groups in terms of quantitative data, independent-samples t-test was used together with Bootstrap results, while the Mann-Whitney U test was used with Monte Carlo simulation technique. Fisher's exact test results were used to compare categorical data, while the Fisher-Freeman-Halton test was used with Monte Carlo simulation results. The correlation analysis of the variables was performed by Spearman's rho test. Quantitative variables are expressed as

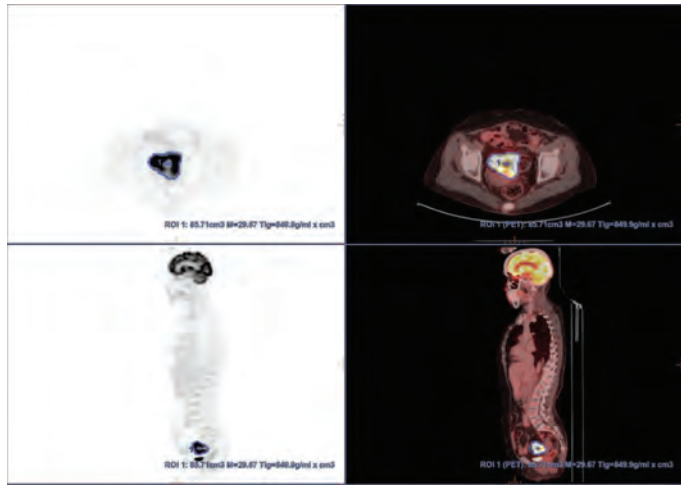

Figure 1. A 39-year-old female patient with sigmoid colon adenocarcinoma. Primary tumor metabolic tumor volume, 85.71 cm³; primary tumor total lesion glycolysis, 849.9 g/mL × cm³; primary tumor SUV_{max}, 29.67; carcinoembryonic antigen, 47.4 ng/mL
SUV_{max}: Maximum standardized uptake value

mean ± standard deviation and median (minimum-maximum), and categorical variables are shown as n (%). Variables were examined at a 95% confidence level, and $p<0.05$ was considered significant.

RESULTS

CEA was positive in 43 (49.4%) patients (Table 1). No significant difference was noted in CEA positivity with respect to age and gender (p=0.150, p=0.811, respectively). The site of the primary lesion was distributed as follows: Rectum, 40 (46%) cases; sigmoid colon, 19 (21.8%) cases; ascending colon, 14 (16.1%) cases; descending colon, 9 (10.3%) cases; transverse colon, 3 (3.4%) cases; hepatic flexure, 1(1.1%) case; and descending-sigmoid colon junction, 1 (1.1%) case (Table 1).

No significant association was noted between the intestinal segment involving the primary lesion and CEA positivity (p=0.878). No significant difference was also noted among SUV_{max}, MTV, and TLG values of the primary tumor and CEA positivity (p=0.611, p=0.980, p=0.527, respectively) (Table 1).

No significant correlation was found in Spearman's correlation test between CEA levels and PET parameters ($p>0.05$) (Table 2).

DISCUSSION

Few studies have compared serum levels of CEA and volume-based PET/CT parameters in patients with colorectal cancer, and most of these have focused on evaluation of recurrence (9,10). Thus, in the present study, we aimed to determine the

Table 1. Comparison of CEA positivity and negativity with age, gender, lesion site, metabolic parameters, and volume-based PET/CT parameters

	CEA			p
	Total	-	+	
	(n=87)	(n=44)	(n=43)	
	Mean ± SD	Mean ± SD	Mean ± SD	
Age	56.7±15.44	54.3±14.78	59.1±15.91	0.150[t]
	n (%)	n (%)	n (%)	
Gender				
Female	23 (26.4)	11 (25.0)	12 (27.9)	0.811[fe]
Male	64 (73.6)	33 (75.0)	31 (72.1)	-
Lesion location				
Ascending colon	14 (16.1)	8 (18.2)	6 (14.0)	0.878[ff]
Hepatic flexure	1 (1.1)	1 (2.3)	0 (0.0)	-
Descending colon	9 (10.3)	4 (9.1)	5 (11.6)	-
Descending colon-sigmoid	1 (1.1)	0 (0.0)	1 (2.3)	-
Rectum	40 (46.0)	21 (47.7)	19 (44.2)	-
Sigmoid colon	19 (21.8)	8 (18.2)	11 (25.6)	-
Transverse colon	3 (3.4)	2 (4.5)	1 (2.3)	-
	Median (min-max)	Median (min-max)	Median (min-max)	
Primary TM MTV	34.8 (3.2-256)	32.935 (3.2-183)	34.8 (3.43-256)	0.980[u]
Primary TM TLG	263.7 (12.3-3164)	240.65 (13.1-2642)	332.9 (12.3-3164)	0.527[u]
Primary TM SUV_{max}	17.7 (6.3-62.8)	16.82 (6.7-62.8)	18.4 (6.3-42.2)	0.611[u]

[t]Independent-samples t-test (Bootstrap), [fe]Fisher exact test (exact), [ff]Fisher-Freeman-Halton test (Monte Carlo), [u]Mann-Whitney U test (Monte Carlo), CEA: Carcinoembryonic antigen, SD: Standard deviation, Min: Minimum, Max: Maximum, MTV: Metabolic tumor volume, PET/CT: Position emission tomography/computed tomography, SUV_{max}: Maximum standardized uptake value, TLG: Total lesion glycolysis, TM: Tumor

Table 2. Correlation between CEA level and metabolic and volume-based PET/CT parameters

	Primary tumor MTV		Primary tumor TLG		Primary tumor SUV_{max}	
	r	p	r	p	r	p
CEA U/mL	0.034	0.758	0.119	0.272	0.149	0.168

Spearman correlation, CEA: Carcinoembryonic antigen, SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

relationship between tumor load and CEA positivity by comparing CEA positivity and volume-based PET/CT parameters of patients with colorectal cancer in the preoperative period.

In the present study, CEA positivity was not associated with age and gender. Moreover, the sensitivity of serum CEA level in the diagnosis of colorectal cancer was 49.4%. In a previous study, Dbouk et al. (11) reported that CEA had diagnostic sensitivity of 58.3%, which was relatively higher than our findings. This difference was considered due to the difference in the cutoff values for CEA positivity used in our study (5 ng/mL) and in their study (3.8 ng/mL) and the fact that a higher sensitivity is expected with the use of lower cutoff values (11).

In the present study, 46% of the tumoral lesions were detected in the rectum, 33.2% in the descending-sigmoid colon junction, 3.4% in the transverse colon, 1.1% in the hepatic flexure, and 16.1% in the ascending colon. Similarly, Siregar and Sibarani (12) evaluated tumor localization in colorectal cancer and reported that lesions were predominantly located in the rectum and left-sided colon.

Moreover, we observed no significant correlation between CEA positivity and the intestinal segment of the primary lesion. Siregar and Sibarani (12) reported that the highest CEA level was found in the rectum among the segments of the large intestine. Although their results appear different from our findings, the data compared are not exactly the same.

^{18}F-FDG PET/CT is now considered a powerful tool for the evaluation and follow-up of patients with cancer. In a retrospective study, Shi et al. (6) examined 107 patients and found that the SUV_{max} value and TNM classification obtained in PET/CT were independent predictors of survival, while SUV_{max} values ≤11.85 were associated with better survival. However, another study showed that a high SUV_{max} value in patients with resectable colorectal cancer was not significantly related with tumor recurrence and disease-free survival (13). The tumor markers CEA and CA 19-9 were also considered to show low diagnostic performance, while high CA 19-9 levels along with PET/CT use were considered to indicate poor prognosis (14). Vallam et al. (15) reported that PET/CT is a significant tool in the detection of recurrent disease during follow-up, independent of serum CEA levels, and the probability of disease recurrence is directly proportional to the value of the increased CEA level. Another study reported the recurrence rates of 10%, 45%, 70%, 94%, and 100% for serum CEA levels of <5, 5.1-10, 10.1-15, 15.01-50, and >50 ng/mL, respectively (16). In addition, PET/CT scan performed in all of these patients revealed sensitivity, specificity, positive predictive, and negative predictive values of 92.7%, 95.2%, 96.2%, and 90.9%, respectively (15).

The consensus report by the College of American Pathologists in 1999 accepted that the tumor volume did not have a prognostic significance (category 4), but serum CEA levels gained prognostic significance (category 1) (16).

Limited studies have shown the correlation between volume-based PET/CT parameters and tumor markers. In a study of 489 patients, Kim et al. (17) did not find a correlation between pretreatment serum CEA levels and tumor volume on magnetic resonance. Similarly, in our study, no significant correlation was found between the preoperative serum CEA level and MTV, TLG, and SUV_{max} values of the primary tumor. However, similar to previous reports, our findings indicate the likelihood of serum CEA levels to increase in the preoperative period (12,18). Although some studies have reported that CEA positivity is not related to the tumor, tumor diameter, and TNM classification, many studies have stated that the preoperative serum CEA levels are related to the prognosis (18-22). In a retrospective study of patients with stage 2 colorectal carcinoma, Spindler et al. (19) revealed that serum CEA levels were considered to change the risk classification by contributing to the distinctive features of patients and help the management of additional treatments. In addition, Margalit et al. (20) evaluated patients with stage I and II colon cancer and stated that serum CEA level ≥2.35 ng/mL can be used to predict the prognosis (13). In another study, preoperative CEA levels ≥5 ng/mL were reported to be independent prognostic factor for overall survival, disease-free survival, and recurrence detection and to be associated with a high risk of mortality (21,22).

Although the combined use of serum CEA levels and imaging methods increases the diagnostic sensitivity of colorectal carcinomas, many recent studies have found that postoperative serum CEA levels are clinically more valuable than its preoperative levels (23-25). Caglar et al. (10) analyzed patients with recurrent colorectal cancer and reported that all quantitative PET/CT parameters (i.e., SUV_{max}, TLG, and MTV) demonstrate a positive correlation with serum CEA levels (10).

Study Limitations

This study is limited by its retrospective design, small number of patients, and lack of data on comparison between benign and malign lesions in terms of CEA positivity.

CONCLUSION

In conclusion, our findings revealed no significant correlation between CEA positivity and volume-based PET/CT parameters (MTV and TLG) in the preoperative period of colon cancer. Although CEA positivity is considered useful in predicting recurrence in the postoperative period and is associated with

tumor burden, it has low diagnostic efficacy in the preoperative period independent of tumor burden.

Ethics

Ethics Committee Approval: Permission was obtained from the Institutional Ethics Committee of the University Health Science Turkey of Gazi Yasargil Training and Research Hospital for the use and publication of patient data (protocol no: 435/2020).

Informed Consent: Before PET/CT, we routinely obtain informed consent from the patient or a relative of patient and ask whether they consent to their data being used anonymously in retrospective medical studies, and our patients in this study are patients who approve this.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Y.G., C.C., Design: Y.G., C.G., C.C., Data Collection or Processing: Y.G., C.G., Analysis or Interpretation: Y.G., C.G., C.C., Literature Search: C.G., C.C., Writing: Y.G., C.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Gold P, Freedman SO. Specific carcinoembryonic antigens of the human digestive system. J Exp Med 1965;122:467-81.
3. Thompson JA, Grunert F, Zimmermann W. Carcinoembryonic antigen gene family: molecular biology and clinical perspectives. J Clin Lab Anal 1991;5:344-66.
4. Wang JY, Lu CY, Chu KS, Ma CJ, Wu DC, Tsai HL, et al. Prognostic significance of pre- and postoperative serum carcinoembryonic antigen levels in patients with colorectal cancer. Eur Surg Res 2007;39:245-50.
5. Herbertson RA, Lee ST, Tebbutt N, Scott AM. The expanding role of PET technology in the management of patients with colorectal cancer. Ann Oncol 2007;18:1774-81.
6. Shi D, Cai G, Peng J, Li D, Li X, Xu Y, et al. The preoperative SUVmax for (18)F-FDG uptake predicts survival in patients with colorectal cancer. BMC Cancer 2015;15:991.
7. Can C. Correlation of (18F) FDG PET/CT Parameters with Haematological Parameters in Esophageal Cancers and the Effect of These Parameters on Survival. Dicle Med J 2020;47:556-67.
8. Akdeniz N, Küçüköner M, Kaplan MA, Urakçı Z, Karhan O, Yerlikaya H, et al. The Effect of Metabolic PET Parameters on Survival Outcome in Malignant Pleural Mesothelioma. Dicle Med J 2020;47:16-23.
9. Ince S, Okuyucu K, Hancerliogulları O, Alagoz E, San H, Arslan N. Clinical Significance of Fluorine-18-fluorodeoxyglucose Positron Emission Tomography/computed Tomography in the Follow-up of Colorectal Cancer: Searching off Approaches Increasing Specificity for Detection of Recurrence. Radiol Oncol 2017;51:378-85.
10. Caglar M, Yener C, Karabulut E. Value of CT, FDG PET-CT and serum tumor markers in staging recurrent colorectal cancer. Int J Comput Assist Radiol Surg 2015;10:993-1002.
11. Dbouk HA, Tawil A, Nasr F, Kandakarjian L, Abou-Merhi R. Significance of CEA and VEGF as Diagnostic Markers of Colorectal Cancer in Lebanese Patients. Open Clin Cancer J 2007;1:1-5.
12. Siregar GA, Sibarani H. Comparison of Carcinoembryonic Antigen Levels Among Degree of Differentiation and Colorectal Cancer's Location in Medan. Open Access Maced J Med Sci 2019;7:3447-50.
13. Lee JE, Kim SW, Kim JS, Choi KY, Kang WK, Oh ST, et al. Prognostic value of 18-fluorodeoxyglucose positron emission tomography-computed tomography in resectable colorectal cancer. World J Gastroenterol 2012;18:5072-7.
14. Odalovic S, Stojiljkovic M, Sobic-Saranovic D, Pandurevic S, Brajkovic L, Milosevic I, et al. Prospective study on diagnostic and prognostic significance of postoperative FDG PET/CT in recurrent colorectal carcinoma patients: comparison with MRI and tumor markers. Neoplasma 2017;64:954-61.
15. Vallam KC, Guruchannabasavaiah B, Agrawal A, Rangarajan V, Ostwal V, Engineer R, et al. Carcinoembryonic antigen directed PET-CECT scanning for postoperative surveillance of colorectal cancer. Colorectal Dis 2017;19:907-11.
16. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000;124:979-94.
17. Kim YJ, Park SC, Kim DY, Moon SH, Chang HJ, Park JW, et al. No correlation between pretreatment serum CEA levels and tumor volume in locally advanced rectal cancer patients. Clin Chim Acta 2012;413:511-5.
18. Topdagi O, Timuroglu A. Evaluation of the Relationship between Carcinoembryonic Antigen and TNM Stage in Colorectal Cancer. Eurasian J Med 2018;50:96-8.
19. Spindler BA, Bergquist JR, Thiels CA, Habermann EB, Kelley SR, Larson DW, et al. Incorporation of CEA Improves Risk Stratification in Stage II Colon Cancer. J Gastrointest Surg 2017;21:770-7.
20. Margalit O, Mamtani R, Yang YX, Reiss KA, Golan T, Halpern N, et al. Assessing the prognostic value of carcinoembryonic antigen levels in stage I and II colon cancer. Eur J Cancer 2018;94:1-5.
21. Baqar AR, Wilkins S, Staples M, Angus Lee CH, Oliva K, McMurrick P. The role of preoperative CEA in the management of colorectal cancer: A cohort study from two cancer centres. Int J Surg 2019;64:10-5.
22. Woo J, Kim J, Park I, Cho H, Gwak G, Yang KH, et al. Perioperative Serum Carcinoembryonic Antigen Ratio Is a Prognostic Indicator in Patients With Stage II Colorectal Cancer. Ann Coloproctol 2018;34:4-10.
23. Kim NH, Lee MY, Park JH, Park DI, Sohn CI, Choi K, et al. Serum CEA and CA 19-9 Levels are Associated with the Presence and Severity of Colorectal Neoplasia. Yonsei Med J 2017;58:918-24.
24. Zhang B, Sun Z, Song M, Ma S, Tian Y, Kong Q. Ultrasound/CT combined with serum CEA/CA19.9 in the diagnosis and prognosis of rectal cancer. J BUON 2018;23:592-7.
25. Beom SH, Shin SJ, Kim CG, Kim JH, Hur H, Min BS, et al. Clinical Significance of Preoperative Serum Carcinoembryonic Antigen Within the Normal Range in Colorectal Cancer Patients Undergoing Curative Resection. Ann Surg Oncol 2020;27:2774-83.

ORIGINAL ARTICLE

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Investigation of Allergy Management in Primary Care: Child vs. Adult Prescriptions

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Abstract

Objective: Allergic diseases are conditions that are frequently encountered in primary care, and different drug groups can be used in their treatment. This study aimed to compare the use of drugs in allergy in children and adults applied to primary care.

Methods: We analyzed prescriptions written by those who were selected by systematic sampling (n=1431) among family physicians serving in İstanbul between January 1 and December 31, 2016. Among these, single-diagnosis prescriptions containing "T78.4-allergy, unspecified" were included in the study, and the prescriptions were divided into those written to children (<18 years old) and adults (≥18 years old). The demographic characteristics of the patients and drug details in the prescriptions were compared according to the groups.

Results: A total of 37,042 prescriptions with a single diagnosis of allergy were identified, and 55.9% of which were for adults. Allergy diagnosis was higher in men (52.4%) among children and in females (67.7%) among adults. Antihistamines (85.3% and 83.4%, p<0.001), systemic steroids (5.4% and 1.6%, p<0.001), and inhalants (1.8% and 1.3%; p<0.001) were more likely prescribed to adults, whereas topical drugs were prescribed more in children (51.7% and 42.7%, p<0.01). Monotherapy was more preferred in children (45.8%) than in adults (41.6%, p<0.0001). Although antihistamine monotherapy was similar in these groups, topical drug monotherapy was used more in children (10.3%) than in adults (5.6%). Prescriptions with first-generation antihistamines were higher in adults (6.8%) than in children (5.4%; p<0.001). Desloratadine was the most commonly encountered drug in the prescriptions of both pediatric and adult patients (21.2% and 10.3%, respectively).

Conclusion: The study revealed that antihistamines, mostly second-generation agents, are frequently preferred. Apart from the higher prescription of systemic corticosteroids for adults and topical drugs for children, it is understood that the pharmacological management of allergic conditions in primary care shows overall similarities in both age groups.

Keywords: Allergy, family physicians, pediatrics, adults, antihistamines, topical drugs

INTRODUCTION

Allergic diseases, which are a frequent reason for morbidity worldwide, pose a significant burden on healthcare systems. It was reported that nearly 30% of the population has been affected by allergy and allergy-related disorders and this might increase up to 80% in terms of families (1). It is common for patients to seek medical advice from primary care for their allergic conditions. Although primary care physicians are expected to manage allergic diseases appropriately, several studies in the literature showed an inadequate knowledge level with some degree of incompetency in rationally implementing the pharmacotherapy based on relevant guidelines (2-4).

Compared with adults, children require a more delicate approach in drug use and represent a special patient population whose

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dynamic physiology involves different pharmacokinetic and pharmacodynamic processes (5,6). Therefore, drug utilization patterns may vary for adult and pediatric populations even in the same indication. Apart from the incidence, disease severity, and prognosis, therapeutic responses may also differ by these age groups (6,7). Moreover, it is well recognized that allergic diseases are more common during childhood (8,9).

About 8% of primary care visits consisted of allergic conditions (10). The disease course, outcome, and pharmacotherapy practice may be different in child and adult age groups (5,11,12). Although encountered by primary care physicians often, no comprehensive study has been reflected in the literature about prescribing practices in allergy for different age groups in Turkey. In this study, we aimed to compare drug use in children versus adults who had allergy diagnoses in primary care.

METHODS

We performed a cross-sectional study where we examined prescriptions of primary care physicians between January 1 and December 31, 2016, in İstanbul. The data were collected after being approved by the non-interventional Ethics Committee of İstanbul Medipol University (approval no: 13.11.2017-521).

Of the 4.293 primary care physicians working in İstanbul, 1.431 were selected using 3:1 systematic sampling. The prescriptions with the solo diagnosis of "T78.4-allergy-unspecified" were examined retrospectively. The prescriptions with multiple diagnoses that contained allergy were not included to ensure that the specified drugs were only prescribed for allergy and, hence, to assess the appropriateness of allergy pharmacotherapy. These prescriptions were further stratified into two groups by their age groups as children (<18 years old) and adults (≥18 years old).

Prescriptions generated for children and adults with allergy diagnoses were compared in terms of the mean age, gender, and monthly distribution. The number of drug items and boxes per encounter was also compared between these two age groups. The percentages of antihistamine agents, topical drugs, systemic corticosteroids, inhalants, and systemic anti-infectives in these prescriptions were identified and compared. In addition, monthly prescribing of antihistamines, systemic corticosteroids, and topical preparations were compared between children and adults. The most prescribed single agents of these drug classes were determined for each age group. The most commonly prescribed 10 drugs were identified in the child and adult groups. The percentage of patients who required systemic antihistamine plus corticosteroid combination was compared between the study groups. Furthermore, the percentage of prescriptions that contained first- and second-generation antihistamine drugs was also compared.

Statistical Analysis

We used Microsoft Office Excel 2016 and SPSS 24.0 for data analysis. Descriptive data were presented as the number and percentages or the mean and standard deviations, where appropriate. We compared the study groups via t-test and Mann-Whitney U test for normally and non-normally distributed continuous variables, respectively, and chi-square test for categorical variables. An overall 5% type-I error level was used to infer statistical significance.

RESULTS

We identified 37,042 prescriptions with a single "T78.4-allergy" diagnosis. The prescriptions generated constituted 44.1% (n=16,342) for children and 55.9% (n=20,700) for adults. The mean ages of children and adults were 6.7±4.5 and 47.3±17.8 years, respectively. The percentage of male gender in children (52.4%) was significantly higher than in adults (32.3%, $p<0.001$). We detected a total of 74,380 drugs in these prescriptions, where the mean number of drug items and boxes per prescriptions was significantly lower in children (1.8±1.0 and 2.1±1.6) than in adults (2.2±1.5 and 3.4±4.1; $p<0.001$ for each). The prescriptions with allergy diagnoses were most commonly generated in January for both children (12.0%) and adults (17.8%), and the lowest percentages were detected in December in both groups (6.0% and 5.0%, respectively).

Antihistamines (85.3% and 83.4%, $p<0.001$), systemic steroids (5.4% and 1.6%, $p<0.001$), and inhalants (1.8% and 1.3%, $p<0.001$) were more likely prescribed to adults, whereas topical drugs were prescribed more in children (51.7% and 42.7%, $p<0.01$). Allergic conditions were managed with monotherapy in 43.5% of all prescriptions, which was significantly higher in children (45.8%) than in adults (41.6%, $p<0.0001$). About three-quarters (75.9%) of the monotherapy included antihistamines (33.0% of all prescriptions), followed by topical agents (17.6% of monotherapy and 7.6% of total). Although antihistamine monotherapy was similar between children (33.0%) and adults (32.9%, $p=0.81$), topical drug monotherapy was more preferred in children (10.3%) than in adults (5.6%; $p<0.0001$). The prescriptions with first-generation antihistamines were higher in adults (6.8%) than in children (5.4%; $p<0.001$; Figure 1). The need for systemic antihistamine plus corticosteroids co-prescription was significantly higher in adults (3.4%) than in children (1.1%, $p<0.001$). The percentages of prescriptions

with systemic antibiotics were similar in children (6.4%) and adults (6.7%, p>0.05).

Seasonal distribution of the drug utilization for allergic conditions showed that children were significantly more likely to be prescribed antihistamines between June and September and topical agents throughout the year except March compared with the adult population (Figure 2).

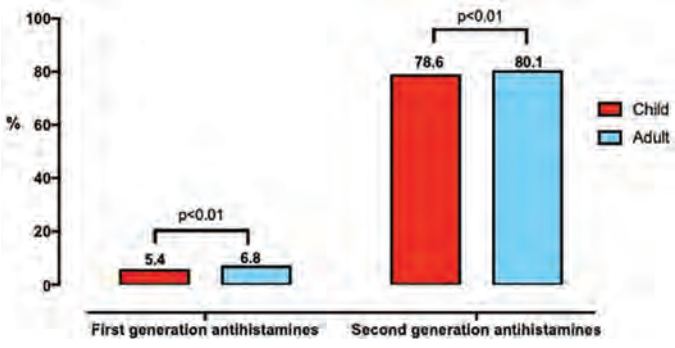

Figure 1. Comparison of prescriptions with first- and second-generation antihistamines between children and adults

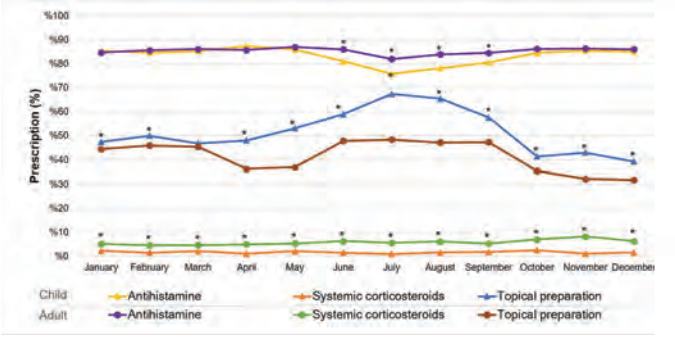

Figure 2. Monthly distribution and comparison of prescriptions with antihistamines, topical preparations, or systemic corticosteroids between children and adults. *p<0.05

The most commonly prescribed antihistamine was desloratadine in both children (45.3%) and adults (25.1%). "lidocaine ± combinations" was the most commonly prescribed topical agent in these age groups (39.6% and 21.0%, respectively). Furthermore, methylprednisolone was the most commonly preferred systemic corticosteroid in children (53.1%) and dexamethasone in adults (45.3%). The most commonly encountered systemic anti-infective in allergy prescriptions were amoxicillin + enzyme inhibitor in both groups (41.9% and 31.4%; Table 1). Desloratadine was the most commonly encountered drug in the prescriptions of both pediatric and adult patients (21.2% and 10.3%, respectively), followed by cetirizine (16.2% and 7.7%, respectively). The third top-used drug was topical lidocaine ± combinations in children (12.4%) compared with rupatadine in adults (7.7%; Figure 3).

DISCUSSION

In this study, we compared pharmacotherapy practices of primary care physicians for unspecified allergy indications in children versus adults. We observed that allergic diseases were rather managed by combination therapies mostly with second-generation antihistamines with higher prescription rates of

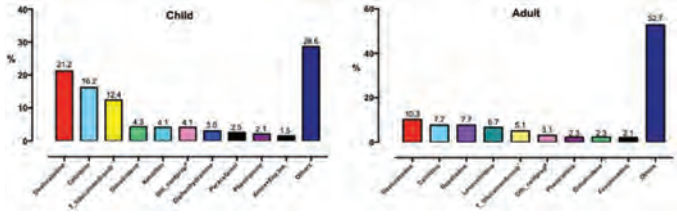

Figure 3. Distribution of all prescribed drugs for children and adults in allergy indication. *Topical lidocaine and combinations, #other common cold preparations

Table 1. Distribution of the most frequently prescribed drugs for child and adult groups

	Ranking	Child (%)	Adult (%)
Antihistamines	1	Desloratadine (45.3)	Desloratadine (25.1)
	2	Cetirizine (34.7)	Cetirizine (18.8)
	3	Ketotifen (8.7)	Rupatadine (18.7)
Topical medication	1	Lidocaine and combinations (39.6)	Lidocaine and combinations (21.0)
	2	Dimetindene (13.6)	Dimetindene (9.3)
	3	Diphenhydramine (9.4)	Corticosteroid + imidazole/triazole (4.1)
Systemic corticosteroids	1	Methylprednisolone (53.1)	Dexamethasone (45.3)
	2	Dexamethasone (41.3)	Methylprednisolone (36.9)
	3	Prednisolone (1.8)	Betamethasone (11.9)
Systemic anti-infectives	1	Amoxicillin + enzyme inhibitor (41.9)	Amoxicillin + enzyme inhibitor (31.4)
	2	Clarithromycin (24.4)	Clarithromycin (14.8)
	3	Cefuroxime (5.4)	Cefuroxime (11.4)

topical agents in children and of systemic corticosteroids in adults.

With a wide spectrum from dermatitis to asthma or allergic rhinitis to anaphylaxis, allergic conditions have been reported to mostly affect the pediatric population (8,9). Contrarily, our study showed a slight predominance of adults with a prescription containing an allergy diagnosis. This might be attributed to the higher utilization of primary care services by adult patients (13). Another factor might be that we only included diagnoses with unspecified allergies since children tend to manifest with symptoms of specific allergic diagnoses like asthma or rhinitis (14). Studies on the relationship between atopy and gender reported higher prevalence in men until adolescence, after which female predominance ensues under the impact of immunosuppressive testosterone and proinflammatory female sex steroids (15). In our study, the boys:girls ratio was 1.1:1 in children compared with the female:male ratio of 2:1 in adults. A primary care study performed at the national level in our country in the same year showed healthcare utilization in favor of boys by 1.1-fold in children and of women by 1.5-fold in adults (13). In this context, it can be suggested that our results may support the female predominance in allergic conditions in the adult population.

One of the mainstay pharmacological groups in managing allergic diseases is oral antihistamines (16,17). The preference of antihistamines as first-line drugs for allergy indications was reported by an international survey study of primary care (2). Although slightly more pronounced in adults, both groups in our study showed frequent prescriptions of antihistamines. Although prescribing of antihistamines exhibited a similar pattern throughout the year in both groups (featuring peaks at spring months), it appears remarkable that the difference was significant during summer months. In addition, both groups mostly revealed prescriptions of second-generation antihistamines (about 80%)-desloratadine and cetirizine-which might be regarded as non-sedating agents. Accordingly, preference of new generation antihistamines over first-generation drugs could be accepted as an overall rational prescribing practice as the latter is less safe (18). In addition, these first-generation drugs were prescribed less in children (5.4%) than in adults (6.8%). The fact that markedly sedative antihistamines may impair cognitive functions thereby resulting in diminished school performance (17) might also partially support the rationality of the physicians in our study in selecting new generation agents with a better safety profile. On the other hand, first-generation antihistamines also convey several risks in adults, for example, negative impacts on vehicle-device use (19). Our findings suggest that primary care physicians may tend to have a more cautious approach in children versus in adults, considering the risks relevant to antihistamines.

Corticosteroids have been used for the management of inflammatory and allergic diseases for more than 50 years. Nevertheless, their systemic use in allergic conditions remains controversial because of their adverse effects and compelling tolerability profiles (20,21). Primary care physicians were reported to often prescribe systemic corticosteroids of short duration in several indications (22). Our study showed that prescriptions containing systemic corticosteroids for pediatric allergic diseases constituted near one-fifth of that in adults, although we did not have the duration of use. Unlike in adults, even the short use of corticosteroids was associated with hypothalamic-hypopituitary-adrenal axis suppression in up to 81% of children (23,24). Although our study revealed a comparably lower rate of corticosteroid use (1.6%) in children, the fact that nearly half of these agents were potent agents (i.e., dexamethasone) may suggest that such axis suppression should be considered more cautiously by physicians. This warrants further prospective research encompassing the dose and duration of corticosteroids.

Urticaria and eczema are common manifestations of allergic diseases (25). Therefore, it would be no surprise to encounter topical drugs in the symptomatic management of allergy in clinical practice. In fact, we observed a topical form in near two prescriptions, with the most frequent being topical lidocaine or its combinations in both children and adults. It is noticeable that, however, more children than adults were prescribed topical agents almost throughout the year. It might be partly attributed to the fact that challenging management of systemic agents in children due to different pharmacokinetics and pharmacodynamics might have directed physicians to prefer topical agents (5). In addition, the highest prescribing of topical agents in the summer months in both age groups may indicate a higher prevalence of insect-bite-induced allergic conditions (26).

The irrational use of antibiotics is a well-known prioritized issue of the health authority for about 10 years. Although some progress has been made owing to ongoing well-structured efforts, irrational antibiotic prescribing was often reported in terms of inappropriate indications or doses (27-29). Allergic diseases do not require the use of systemic anti-infectives unless an underlying or secondary condition entails. One of the reasons we only included the prescriptions with a solo diagnosis of allergy was to omit the rationale of prescribing antibiotics for probable secondary indications. However, it is remarkable that 7% of prescriptions with merely allergy diagnoses contained systemic anti-infective drugs both in children and adults. Furthermore, most of these agents were the amoxicillin + enzyme inhibitor, a broad-spectrum antibiotic. This substantial rate of inappropriate

prescribing practice might provide additional critical insight for the action plans on rational antibiotic use.

The findings of our study need to be interpreted in light of its limitations. The study sample only included the prescriptions with the diagnosis of "T78.4-allergy, unspecified". Therefore, we were unable to distinguish details of drug utilization in specific allergic reactions such as urticaria, angioedema, drug/food allergy, and insect bite, which might be listed under this unspecified indication yet managed differently. In addition, the diagnoses established by primary care physicians are regarded as definite without any further verification. Several drugs for allergic conditions, for example, some inhalants for bronchial asthma, were initiated by secondary or tertiary care physicians and managed in primary care as part of the repeated prescription practice. Such conditions might not have reflected the actual practice of primary care of allergy. Besides, we did not evaluate the detailed use of certain drug classes in specified age groups, that is, first-generation antihistamines above 65 years in adults or in school-age groups among children, which may reflect a potential of inappropriate use in clinical practice. Finally, the findings on the seasonal distribution of drug use should be carefully approached as it only represented prescriptions in 2016.

CONCLUSION

It was the first time to reveal the similarities and differences of the pharmacological management of allergy in primary care between children and adults. Although these age groups differ in terms of gender predominance, the pharmacotherapy of unspecified allergic conditions appears to be similar for children and adults, albeit with several nuances. Allergy in primary care was mostly managed by second-generation antihistamines, where one in every two patients was prescribed additional topical agents. Remarkably, the age groups featured higher prescription rates of systemic corticosteroids for adults and topical drugs for children. We believe that the findings of our study provided insights and made contributions to studies on the rational management of allergic conditions in different populations and the functionality of treatment algorithms from a primary care perspective.

Ethics

Ethics Committee Approval: The data were collected after being approved by the non-interventional Ethics Committee of İstanbul Medipol University (approval no: 13.11.2017-521).

Informed Consent: Not applicable for this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: V.A., N.İ.K., Ö.A., N.A., A.A., Design: V.A., N.İ.K., A.A., Data Collection or Processing: V.A., N.A., Analysis or Interpretation: V.A., N.İ.K., Literature Search: V.A., N.İ.K., N.A., Writing: V.A., N.İ.K., Ö.A., N.A., A.A.

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REFERENCES

1. Sánchez-Borges M, Martin BL, Muraro AM, Wood RA, Agache IO, Ansotegui IJ, et al. The importance of allergic disease in public health: an iCAALL statement. World Allergy Organ J 2018;11:8.
2. Agache I, Ryan D, Rodriguez MR, Yusuf O, Angier E, Jutel M. Allergy management in primary care across European countries -- actual status. Allergy 2013;68:836-43.
3. Uygunsoy M, Mevsim V. Diagnostic Tests in The Management of Allergic Diseases in Primary Care. Turkish J Fam Med Prim Care 2020;14:141-6.
4. Baldacci S, Maio S, Simoni M, Cerrai S, Sarno G, Silvi P, et al. The ARGA study with general practitioners: impact of medical education on asthma/rhinitis management. Respir Med 2012;106:777-85.
5. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med 2003;349:1157-67.
6. Kırmızı Nİ, Aydın V, Akıcı N, Akıcı A. Çocuklarda Endikasyon Dışı İlaç Kullanımı. J Lit Pharm Sci 2020;9:149-57.
7. World Health Organization. Promoting Safety of Medicines for Children, 2007. ISBN: 9789241563437.
8. Gupta R, Sheikh A, Strachan DP, Anderson HR. Burden of allergic disease in the UK: secondary analyses of national databases. Clin Exp Allergy 2004;34:520-6.
9. Anandan C, Gupta R, Simpson CR, Fischbacher C, Sheikh A. Epidemiology and disease burden from allergic disease in Scotland: analyses of national databases. J R Soc Med 2009;102:431-42.
10. Diwakar L, Cummins C, Lilford R, Roberts T. Systematic review of pathways for the delivery of allergy services. BMJ Open 2017;7:e012647.
11. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008;122(2 Suppl):S1-84.
12. Jutel M, Papadopoulos NG, Gronlund H, Hoffman HJ, Bohle B, Hellings P, et al. Recommendations for the allergy management in the primary care. Allergy 2014;69:708-18.
13. Bayram D, Vızdıklar C, Aydın V, İşli F, Akıcı A. Birinci basamakta reçeteleme trendi ve sık karşılaşılan tanılara ait reçetelerin incelenmesi: Türkiye verisi. Cukurova Med J 2020;45:695-708.

14. Thomsen SF. Epidemiology and natural history of atopic diseases. Eur Clin Respir J 2015;2.

15. Osman M. Therapeutic implications of sex differences in asthma and atopy. Arch Dis Child 2003;88:587-90.

16. Kuna P, Jurkiewicz D, Czarnecka-Operacz MM, Pawliczak R, Woroń J, Moniuszko M, et al. The role and choice criteria of antihistamines in allergy management - expert opinion. Postepy Dermatol Alergol 2016;33:397-410.

17. Randall KL, Hawkins CA. Antihistamines and allergy. Aust Prescr 2018;41:41-5.

18. Fein MN, Fischer DA, O'Keefe AW, Sussman GL. CSACI position statement: Newer generation H1-antihistamines are safer than first-generation H1-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria. Allergy Asthma Clin Immunol 2019;15:61.

19. Popescu FD. H1 antihistamines and driving. J Med Life 2008;1:262-8.

20. Hox V, Lourijsen E, Jordens A, Aasbjerg K, Agache I, Alobid I, et al. Benefits and harm of systemic steroids for short- and long-term use in rhinitis and rhinosinusitis: an EAACI position paper. Clin Transl Allergy 2020;10:1.

21. Bleecker ER, Menzies-Gow AN, Price DB, Bourdin A, Sweet S, Martin AL, et al. Systematic Literature Review of Systemic Corticosteroid Use for Asthma Management. Am J Respir Crit Care Med 2020;201:276-93.

22. Dvorin EL, Ebell MH. Short-Term Systemic Corticosteroids: Appropriate Use in Primary Care. Am Fam Physician 2020;101:89-94.

23. Streck WF, Lockwood DH. Pituitary adrenal recovery following short-term suppression with corticosteroids. Am J Med 1979;66:910-4.

24. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. Arch Dis Child 2016;101:365-70.

25. Demoly P, Chabane H, Fontaine JF, de Boissieu D, Ryan D, Angier E, et al. Development of algorithms for the diagnosis and management of acute allergy in primary practice. World Allergy Organ J 2019;12:100022.

26. Pansare M, Seth D, Kamat A, Kamat D. Summer Buzz: All You Need to Know about Insect Sting Allergies. Pediatr Rev 2020;41:348-56.

27. Versporten A, Bolokhovets G, Ghazaryan L, Abilova V, Pyshnik G, Spasojevic T, et al. Antibiotic use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe. Lancet Infect Dis 2014;14:381-7.

28. Sahin A, Akici A, Aydin V, Melik B, Aksoy M, Alkan A. Variation of antibiotic consumption and its correlated factors in Turkey. Eur J Clin Pharmacol 2017;73:867-73.

29. OECD (2019), Health at a Glance 2019: OECD Indicators, OECD Publishing: Paris.

ORIGINAL ARTICLE

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Is a First Epileptic Seizure a COVID-19 Finding?

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Abstract

Objective: It is known that coronavirus disease-2019 (COVID-19) can manifest with neurologic findings in addition to respiratory symptoms. This study aimed to investigate the rate of patients with COVID-19 who presented with a first epileptic seizure as a neurologic finding.

Methods: The study included patients who presented to our hospital's emergency department reporting a seizure between March 11 and May 30, 2020. Of 90 patients, 32 (35.5%) presented first seizures. The patients' demographic characteristics, medical history, complications, the presence of risk factors relating to their treatment and seizures, laboratory findings, clinical properties, and imaging findings were recorded.

Results: Of the patients with first seizures, 19 were men, and 13 were women. Their mean age was 49.5 (minimum: 18, maximum: 89) years. The percentage of patients with COVID-19 who presented with a first seizure was 31.2% (n=10). A risk factor was identified in 8 (80%) patients who presented with a first seizure, and no risk factor was found in 2 (20%) patients. In all patients, COVID-19 was diagnosed following a seizure presentation. The intensive care requirement rate was 30% (n=3), and 2 (20%) patients died.

Conclusion: The rate of COVID-19 among patients presenting with a first seizure is high. It would be appropriate to consider patients arriving with a seizure without any other respiratory or systemic issues as being related to COVID-19 and plan the necessary analyses and treatment.

Keywords: COVID-19, SARS-CoV-2, first seizure, epilepsy, neurologic symptom

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a novel infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which first emerged in Wuhan, China, in late 2019. It spread around the globe, causing the World Health Organization to announce a pandemic (1). In addition to systemic and respiratory symptoms, it has been documented that 36.4% (78/214) of patients with COVID-19 developed neurologic symptoms, including headaches, impaired consciousness, and paresthesia (2). Various studies demonstrated that coronaviruses were neurotrophic and neuroinvasive (3). The probability of developing neurologic symptoms is higher in severely affected patients than in those with mild or moderate diseases (2).

The reported symptoms of COVID-19 are primarily related to the respiratory or gastrointestinal systems, and seizures remain in the background (4). As the pandemic developed, it has been found that the disease may manifest without respiratory problems through other systemic findings. Although it has not been reported that the ratio of neurologic comorbidity is greater for COVID-19 than other respiratory viral infectious diseases, prospective data will yield more definite results. In addition to causes such as high temperature being capable of giving rise to seizures in patients with epilepsy infected by COVID-19 or any other infectious disease, seizures may also be triggered by direct virus invasion or through cytokines (5). The effects of COVID-19 on patients with epilepsy or the prevalence of newly emerging epilepsy is still uncertain.

This study aimed to investigate the rate of COVID-19 diagnoses in patients presenting to the emergency department (ED) with primary symptoms of seizures and demonstrate whether seizures might be considered a first finding of COVID-19.

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METHODS

This study is a single-center, retrospective, observational study. The University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital is a tertiary care multidisciplinary hospital where 500,000 to 550,000 patients are treated annually. In our hospital, around 400 patients present daily to our ED pandemic area with suspected COVID-19 infection, and about 40 patients are diagnosed with COVID-19. The study included 90 patients aged over 18 years who presented to our hospital's ED with symptoms of seizure between March 11 and May 30, 2020. For the study, approval was obtained from the University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital Ethics Board (no: 48670771-514.10) and the Ministry of Health. Informed consent was obtained from all patients. The study was compliant with the Helsinki Declaration.

Patients

Patients aged over 18 years who presented to the ED with symptoms of seizure were evaluated. Patients aged under 18 years and those who declined to participate in the study were excluded. The electronic medical records of all recorded cases were registered in the case reporting form. The patients' demographic properties, medical history, complications, and the presence of risk factors for treatments and seizures were obtained. Clinical, laboratory, and imaging findings were evaluated. The following risk factors were considered: Acute cerebrovascular disease, head trauma, central nervous system infection, and metabolic disorder.

Statistical Analysis

The Number Cruncher Statistical System Statistical Software (NCSS Statistical Software Inc., Utah, USA) was used for statistical analysis. To evaluate the data from the study, descriptive statistical methods (mean, standard deviation, median, frequency, and ratio) were used.

RESULTS

The study included 90 patients who presented to the ED with a seizure. Of them, 5 (5.5%) who had an early seizure diagnosis were non-epileptic: 3 syncopes, 1 dystonic spasm related to the adverse effects of medication, and 1 seizure secondary to hypocalcemia. During this process, the rate of patients with known epilepsy who presented to the ED among all cases of epilepsy was 62.35% (n=53), and 35.5% (n=32) presented with a first seizure. Of the first seizure cases, there were 19 men and 13 women. Their mean age was 49.5 (minimum: 18, maximum: 89) years. Of the 32 patients, 14 had definitively eliminated COVID-19, 8 had suspected COVID-19, and 10 were COVID-19-positive (Figure 1). Of the 10 patients diagnosed with COVID-19, 5 were women and 5 men, with a mean age of 56.6±13.48 years.

Of the 10 patients with COVID-19, 6 had focal or secondary generalized and 4 generalized tonic-clonic (GTC). Three patients with focal seizures were sequela of cerebrovascular accidents. Table 1 shows the patients' demographic characteristics, computed tomography scans, and concomitant illnesses. Because the seizures of two patients with focal seizures and one with GTC seizures could not be controlled, they were transferred to the intensive care unit (ICU). All patients were started on levetiracetam as treatment.

Ten patients who presented with a first seizure were diagnosed with COVID-19. Among the first seizures, the rate of patients with COVID-19 from among all seizure symptoms presenting to the ED was 11.7% (n=10). Their rate among patients with first seizures was 31.25% (10/32). Of the patients evaluated with a first seizure and diagnosed with COVID-19, one was a healthy 34-year-old woman who had given birth 1 week ago, one was a 51-year-old man with no features other than a COVID-19 infection, and eight had a seizure-triggering risk factor. The most frequently encountered risk factor was a previous cerebrovascular disease. No severe electrolyte abnormality was observed in any of the patients. There were two patients with chronic kidney dysfunction, and significant increases were found in their creatinine levels.

All patients were diagnosed following the COVID-19 diagnosis and treatment protocol. A polymerase chain reaction (PCR) test was performed on each patient using a nasopharyngeal swab sample. Radiologic appearance compatible with viral pneumonia was found in all patients, and PCR positivity was found in 3 (30%). Lymphopenia was present in 3 (30%) patients,

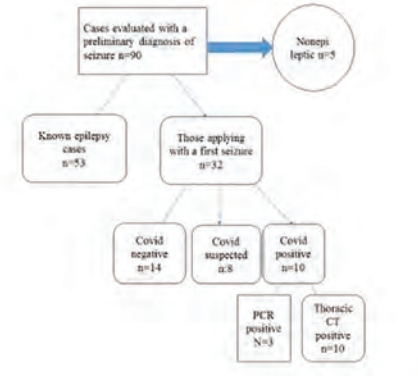

Figure 1. Study table
PCR: Polymerase chain reaction, CT: Computed tomography

high D-dimer levels in 6 (60%), and high C-reactive protein (CRP) levels in 9 (90%; Table 2). Only one patient reported shortness of breath and palpitations.

The mortality rate was also evaluated. A 78-year-old woman who presented with severe COVID-19 findings and had been transferred to the ICU died on the 22nd day. However, she had accompanying comorbid factors such as chronic renal insufficiency, congestive heart failure, diabetes mellitus, hypothyroid, and asthma. Her last CRP and D-dimer values were 262.51 and 1892, respectively. Another 57-year-old woman who had colon carcinoma also died after being discharged.

DISCUSSION

In our study, 10 patients were diagnosed with COVID-19 after performing analyses following a first seizure presentation to the ED. We found that accompanying seizure-triggering comorbidities existed in eight patients, in which a combination of a first seizure and COVID-19 was present. In their study, Lu et al. (6) emphasized that there were seizure-triggering predisposing factors. In two patients with no risk factors, the seizures were considered symptomatic, and treatment was started. These seizures may be a finding brought about by the infection, but they may also be coincidental. There are insufficient data on whether COVID-19 per se is a risk factor. Although there were no risk factors that would lower the seizure threshold in most cases, no seizure was identified previously in any of these cases, who, accordingly, had not received any treatment. During the pandemic, it is important to follow up on patients who present with a first

Table 1. Demographic properties of cases arriving with COVID-19 and a first seizure

Case no.	Gender	Age (years)	Seizure type	History	PCR	Thoracic CT	Brain CT
1	Male	51	GTC	No	Negative	Yes	Normal
2	Female	89	Focal	Sequela CVA	Positive	Yes	Left frontoparietal ischemia
3	Female	64	Focal	Sequela CVA	Negative (3 times)	Yes	Left thalamic infarction
4	Male	37	Focal	Sequela CVA	Negative	Yes	Bilateral cerebral atrofia
5	Female	78	Focal	CHF, CRI, DM hypothyroidism	Negative	Yes	Normal
6	Male	57	GTC	Alcohol abuse	Negative	Yes	Normal
7	Male	37	GTC	HIV, CRI	Positive	Yes	Normal
8	Male	62	Focal	Subacute ischemia	Negative	Yes	Right frontal ischemia
9	Female	34	GTC	No	Negative	Yes	Normal
10	Female	57	Focal	Colon cancer	Positive	Yes	Normal

COVID-19: Coronavirus diease-2019, PCR: Polymerase chain reaction, CHF: Chronic congestive heart failure, CRI: Chronic renal failure, DM: Diabetes mellitus, GTC: Generalized tonic-clonic, HIV: Human immunodeficiency virus, CVA: Cerebrovascular accident, CT: Computed tomography

Table 2. Hematological values

Case no.	WBC	Neutrophil	Lymphocyte	Hb	HCT	Plt	D-dimer	CRP
Normal values	3800-10,000/uL	1780-5380/uL	1320-3570/uL	130-175 g/L	40-52%	150.000-400.000/uL	80-500 ug/L	<5 mg/L
1	8100	6700	1520	121	36.2	310.000	420	5
2	10,630	8480	990	94	30.1	384.000	1320	96.43
3	6730	4370	2230	74	22.9	356.000	1970	26
4	6070	4000	1560	117	35.8	251.000	615	54.24
5	14,300	12,190	1840	87	27.4	280.000	892	218
6	11,430	8150	2120	114	34.2	304.000	495	23.24
7	8160	6990	920	82	24.5	6000	996	21
8	11,600	7500	2780	141	42.9	181.000	500	6.85
9	8320	6500	2100	118	37.4	302.000	430	15
10	2300	1930	230	84	24.7	89.000	548	71.45

WBC: White blood cell, Hb: Hemoglobin, HCT: Hematocrit, Plt: Platelet, CRP: C-reactive protein

seizure concerning COVID-19 and take early precautions (5-7).

Among human coronaviruses, HCoV-229E, HCoV-OC43, HCoVNL63, and HCoV-HKU1 are common and endemic in the world. They are the causative agents of seasonal upper respiratory tract infections such as rhinitis, pharyngitis, and otitis. Sometimes, they can cause bronchitis, bronchiolitis, and asthma attacks. SARS-CoV and the Middle East respiratory syndrome (MERS-CoV) cause more serious respiratory symptoms. In addition to the respiratory symptoms of endemic coronaviruses (MERS-CoV and SARS-CoV), neurologic clinical pictures such as meningitis, encephalitis, Guillain-Barre syndrome, necrotizing encephalopathy, and myelitis are reported. The agent was present in the cerebrospinal fluid (CSF) of patients, and histopathologically, cranial involvements such as viral particles, cerebral edema, ischemic pad, demyelination, and mononuclear cell infiltration were proven in the autopsies of some mortal cases (8,9). The pathobiology of these neuroinvasive viruses is not yet fully known. Accordingly, it is important to study the impacts of CoV infections on the nervous system (10).

Angiotensin-converting enzyme 2 is found on the surfaces of glial cells and neurons, and the CNS may be a potential target of SARS-CoV-2 through this receptor (11). The accumulation of inflammatory markers may cause local cortical damage related to the COVID-19 infection, which triggers seizures (12). Patients with COVID-19 may present with fever, hypoxia, multiple organ failure, and serious metabolic and electrolytic irregularities; therefore, subclinical acute symptomatic seizures are expected in such patients. In some patients, seizures develop as a result of hypoxia, metabolic disorders, organ failure, and even cerebral damage, which may also occur in COVID-19 patients. In addition to data indicating that COVID-19 increases cerebral thrombosis, there are also papers suggesting that it triggers cerebral edema, which, in turn, triggers seizures (13). A study indicated that the cumulative risks of COVID-19 were high in patients diagnosed with epilepsy. In hospitalizations, epilepsy was related to mortality, and these cases were accompanied by high blood pressure (14).

Mao et al. (2) evaluated the neurologic involvement of 214 inpatients and found a neurologic involvement rate of 25%. The rate of epilepsy was 0.5% among these neurologic findings. An electroencephalography (EEG) recording was not made in this study, and the virus was not isolated from the CSF (2). A COVID-19 diagnosis was verified in a patient who presented with meningoencephalitis findings, but the virus could not be isolated from the CSF (15). CSF PCR studies are important to demonstrate neurologic involvement rates accurately. Also, there is a meningitis/encephalitis report relating to SARS- CoV-2. SARS-CoV-2 RNA was found in the CSF, but a nasopharyngeal swab yielded a PCR-negative result (16). In a case report, a 78-year-old female patient presented initially for focal seizures, and then, a SARS-CoV-2 infection was found (17).

CSF positive and negative cases are found in the literature. This, in turn, supports the thought that seizure-triggering mechanisms may be different. A limitation to our cases was that we were unable to take EEGs or perform PCR on the CSF due to the pandemic conditions. We could have presented more valuable data and stronger interpretations if we were able to perform isolations from the CSF of COVID-19 positive patients with no risk factors (18).

In the literature, a patient who presented to the ED reporting cough, fever, and headache was intubated 2 days afterward and was extubated in the ICU after 10 days. However, a non-convulsive status epilepticus (NCSE) diagnosis was given when mental fog continued, despite normal magnetic resonance and CSF examination results. The patient was diagnosed with NCSE and treated with levetiracetam and clobazam (19). In our clinical observation, we provided symptomatic treatment to changes in mental state and agitation, especially inpatients, but we were unable to verify the NCSE distinctive diagnosis in these patients. Even if we had such cases, we were unable to identify them; the cases we examined consisted of epileptic cases with a motor component.

When planning treatment, the interaction of medication used for COVID-19 with antiepileptic medication should be considered. In these patients, levetiracetam treatment was started by considering the drug's adverse effects and interactions. Provided that care is exercised on renal functions, levetiracetam is among the recommended drugs. It is necessary to perform dose adjustment in the event of renal insufficiency. Carbamazepine, lacosamide, phenytoin, and rufinamide may cause cardiac transmission abnormalities (20). It is logical to continue for approximately 6 weeks until the COVID-19 tests yield negative results and then to discontinue them quickly over 1-2 weeks. We will be able to determine the presence of seizures or lack thereof in patients in whom we started treatment only after a long-term follow-up, but for now, we have planned that they should receive antiepileptics for at least 6 months. ICU treatment was necessary for 3 of 10 patients because their seizures could not be controlled.

Study Limitations

The limitations of our study were the low number of patients, the extraordinary circumstances caused by the pandemic, and the fact that CSF examinations and EEG scans were not performed to protect the healthcare personnel on duty. We included only seizures with a motor component in the study. We were unable to diagnose any NCSE, and we probably overlooked it clinically.

CONCLUSION

In conclusion, COVID-19 may rarely present with a seizure, sometimes with no other underlying causes. Prospective long-term studies must be performed to identify the risk of patients with COVID-19 developing seizures or epilepsy in later months or years as a result of their disease. Also, post-mortem autopsy studies will be valuable to identify pathogenesis and involvement rates.

Ethics

Ethics Committee Approval: For the study, approval was obtained from the University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital Ethics Board (no: 48670771-514.10) and the Ministry of Health.

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Ü.Ö., A.K., E.Ü., S.Ü., Concept: S.Ü.Ö., S.Ü., Design: S.Ü.Ö., Data Collection or Processing: S.Ü.Ö., A.K., E.Ü., Analysis or Interpretation: S.Ü.Ö., A.K., E.Ü., Literature Search: S.Ü.Ö., Writing: S.Ü.Ö.

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REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20.
2. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683-90.
3. Hung EC, Chim SS, Chan PK, Tong YK, Ng EK, Chiu RW, et al. Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. Clin Chem 2003;49:2108-9.
4. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239-42.
5. Vohora D, Jain S, Tripathi M, Potschka H. COVID-19 and seizures: Is there a link? Epilepsia 2020;61:1840-53.
6. Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study. Epilepsia 2020;61:e49-e53.
7. Anand P, Al-Faraj A, Sader E, Dashkoff J, Abdennadher M, Murugesan R, et al. Seizure as the presenting symptom of COVID-19: A retrospective case series. Epilepsy Behav 2020;112:107335.
8. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med 2005;202:415-24.
9. Kim JE, Heo JH, Kim HO, Song SH, Park SS, Park TH, et al. Neurological Complications during Treatment of Middle East Respiratory Syndrome. J Clin Neurol 2017;13:227-33.
10. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020;87:18-22.
11. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. ACS Chem Neurosci 2020;11:995-8.
12. Hepburn M, Mullaguri N, George P, Hantus S, Punia V, Bhimraj A, et al. Acute Symptomatic Seizures in Critically Ill Patients with COVID-19: Is There an Association? Neurocrit Care 2021;34:139-43.
13. Kadono Y, Nakamura Y, Ogawa Y, Yamamoto S, Kajikawa R, Nakajima Y, et al. A case of COVID-19 infection presenting with a seizure following severe brain edema. Seizure 2020;80:53-5.
14. Cabezudo-García P, Ciano-Petersen NL, Mena-Vázquez N, Pons-Pons G, Castro-Sánchez MV, Serrano-Castro PJ. Incidence and case fatality rate of COVID-19 in patients with active epilepsy. Neurology 2020;95:e1417-e25.
15. Duong L, Xu P, Liu A. Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in Downtown Los Angeles, early April 2020. Brain Behav Immun 2020;87:33.
16. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 2020;94:55-8.
17. Vollono C, Rollo E, Romozzi M, Frisullo G, Servidei S, Borghetti A, et al. Focal status epilepticus as unique clinical feature of COVID-19: A case report. Seizure 2020;78:109-12.
18. Galanopoulou AS, Ferastraoaru V, Correa DJ, Cherian K, Duberstein S, Gursky J, et al. EEG findings in acutely ill patients investigated for SARS-CoV-2/COVID-19: A small case series preliminary report. Epilepsia Open 2020;5:314-24.
19. Balloy G, Leclair-Visonneau L, Péréon Y, Magot A, Peyre A, Mahé PJ, et al. Non-lesional status epilepticus in a patient with coronavirus disease 2019. Clin Neurophysiol 2020;131:2059-61.
20. Asadi-Pooya AA. Seizures associated with coronavirus infections. Seizure 2020;79:49-52.

ORIGINAL ARTICLE

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Optical Coherence Tomography Findings in Patients with Myotonic Dystrophy Type 1

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Abstract

Objective: Myotonic dystrophy type 1 (DM1) is characterized by myotonia and progressive muscle weakness caused by the cytosine-thymine-guanine trinucleotide repeat and is the most common muscular dystrophy in adults. Although various ocular abnormalities, particularly cataracts, are well known in patients with DM1, few studies and case reports are available on retinal involvement, such as retinal degeneration, the epiretinal membrane (ERM), and macular degeneration. In this study, we investigated the retinal involvement findings using optical coherence tomography (OCT) in patients who were followed up in the neuromuscular outpatient clinic with a diagnosis of DM1.

Methods: In this prospective cross-sectional study, 20 patients with genetically confirmed DM1 aged 18-65 years were included. The control group was formed from healthy individuals of a similar age and gender distribution to the patient group. Patients with diabetes mellitus, diabetic retinopathy, glaucoma, and previous cataract surgery were excluded from the study. Muscular impairment rating (MIR) scales were evaluated according to the distribution findings of myotonia and muscle weakness on a neurological examination. Patients were evaluated with OCT to examine macular and optic nerve morphology after ophthalmologic and fundus examinations were performed by a retinal specialist.

Results: The mean central macular thickness (CMT) values were 275.52±40.31 and 262.76±9.06 in the control and study groups, respectively (p=0.09). Subfoveal choroidal thicknesses (SFCT) were significantly higher in the study group (341.8±95.04 vs. 279.59±46.65; p=0.002). The mean retinal nerve fiber layer did not differ between the groups (103.6±14 vs. 101.3±12; p=0.12). No ERM was detected in any of the DM1 patients. No correlation was found between CMT, SFCT, and the MIR stages ($p<0.05$).

Conclusion: Visual disturbances associated with DM1 may be caused by cataracts as well as retinal disorders. An OCT examination is a beneficial part of the routine ophthalmologic evaluation in DM1 patients.

Keywords: Myotonic dystrophy type 1, OCT, retinopathy, macular degeneration, retina

INTRODUCTION

Myotonic dystrophy type 1 (DM1) is a very rare disease that can involve multiple systems, such as skeletal muscle, heart, smooth muscle, the eyes, or the endocrine and central nervous systems. DM1 exhibits an autosomal dominant inheritance pattern caused by the cytosine-thymine-guanine trinucleotide repeat (1,2). The disease is characterized by myotonia and progressive muscle weakness, and it is the most common muscular dystrophy in adults (1,2). Although various ocular abnormalities, particularly cataracts, are well known in patients with DM1, few studies and case reports are available on retinal involvement, such as retinal degeneration, the epiretinal membrane (ERM), and macular degeneration. In this study, we investigated the retinal involvement findings using optical coherence tomography (OCT) in patients who were followed up in the neuromuscular outpatient clinic with a diagnosis of DM1. As an OCT examination is a fast and non-invasive instrument to search for posterior segment ocular

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pathologies without pupillary dilatation, it might be a helpful tool to investigate the etiology of the visual impairment in DM1 patients.

METHODS

In this prospective cross-sectional study, 20 patients with genetically confirmed DM1 aged 18-65 years who were followed up in the Neuromuscular Outpatient Clinic of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital were included in the study. Patients with diabetes mellitus, diabetic retinopathy (DR), glaucoma, and previous cataract surgery were excluded from the study. A control group was formed from healthy individuals of similar age and gender distribution to the patient group. Demographic and clinical data of the patients, such as age, gender, and disease duration, were noted. The muscle strength examination of the patients involved 11 muscle groups including the bilateral neck flexors. The proximal and distal muscle groups were scored on the medical research council (MRC) (0-5 points) scale by manual muscle testing. Muscular impairment rating (MIR) scales were evaluated according to the distribution findings of myotonia and muscle weakness on the neurological examination (3). Accordingly, the patients were classified into five grades as patients without clinical muscle weakness in grade 1, clinical myotonia without limb weakness and weakness of the face and neck flexors in grade 2, distal weakness in grade 3, mild to moderate (MRC score <5) proximal weakness in grade 4, and severe (MRC score <3) proximal weakness in grade 5.

Patients were evaluated by OCT to examine the macular and optic nerve morphology after ophthalmologic and fundus examinations were performed by a retinal specialist. Macular and retinal nerve thickness measurements were made in both eyes. Choroidal thickness was evaluated using the enhanced depth imaging mode of

spektral domain (SD)-OCT (Spectralis HRA + OCT; Heidelberg Engineering Inc., Heidelberg, Germany). Subfoveal choroidal thickness (SFCT) was measured between the hyperreflective retinal pigment epithelium-Bruch membrane complex and the hyperreflective scleral/choroidal junction (Figure 1). The presence of the ERM and similar pathologies were investigated. The ophthalmological examination findings, biomicroscopic findings, OCT findings [central macular thickness, retinal nerve fiber thickness (RNFL)], and OCT comments were recorded. The characteristics of the DM1 patients and control groups were compared.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 statistical software (SPSS Inc., Chicago, IL, USA). The data were determined to be normally distributed by the Kolmogorov-Smirnov test. Descriptive summary statistics are expressed as means (range and SD) for continuous variables and as frequencies and percentages for categorical variables. The relationships between the categorical data were evaluated with the chi-square test. To compare two independent groups, the Student's t-test was used for normally distributed data, whereas the Mann-Whitney test was used for the not normally distributed data. Spearman's correlation test was used to evaluate the relationship between disease duration and the MIR scale. A p value <0.05 was considered significant.

Ethics committee approval was obtained for the study from University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital Location Ethics Committee (30.06.2020-277). It was made following the principles of the Declaration of Helsinki.

RESULTS

Twenty patients (10 males and 10 females; mean age 36.4±14.5; range 18-65 years) were included in the study group. The mean symptom duration of the patients was 10.8 years. According to the MIR scale, 10% of the patients were grade 1, 25% were grade 2, 25% were grade 3, 20% were grade 4, and 20% were grade 5.

A choroidal neovascular membrane (CNVM) was found in one eye of one patient with retinal pigmentary changes in the fellow eye (Figure 2, 3). In another patient, paracentral acute middle maculopathy (PAMM) secondary to a possible transient arterial obstruction was detected on the OCT scan. A posterior subcapsular cataract was detected in 10% of the patients (n=2). No evidence of ERMs was detected in any of the DM1 patients.

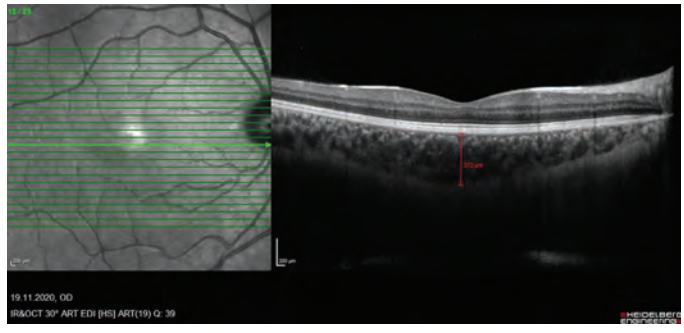

Figure 1. SFCT was measured manually by an experienced retinal physician using an integrated caliper system
SFCT: Subfoveal choroidal thicknesses

When OCT findings were examined in the study patients (40 eyes of 20 patients), the mean central macula thickness (CMT) was 275.52±40.31 µm. The mean CMT in the control group was 262.76±9.06 µm (p=0.09). The mean SFCT differed between the groups significantly (study: 341.8±95.04; control: 279.59±46.65 µm; p=0.002). The mean RNFL values were 103.6±14 and 101.3±12 µm in the study and control groups, respectively (p=0.12).

No significant correlation was found between the MIR stages and the CMT, RNFL, or SFCT values of the study group (p>0.05).

The demographic, clinical, and OCT findings of the study and control groups are shown in Table 1.

DISCUSSION

In this study, the presence of retinal changes in patients with very rare DM1 disease was investigated via SD-OCT examinations. The central macular thickness, vitreoretinal interface, and SFCT were evaluated and compared to an age and sex-matched control group. Kersten et al. (4) reported a higher incidence of ERMs among DM1 patients. However, we did not detect the presence of ERMs in any of our patients. However, the mean SFCT was significantly higher in the DM1 patients than in the control group.

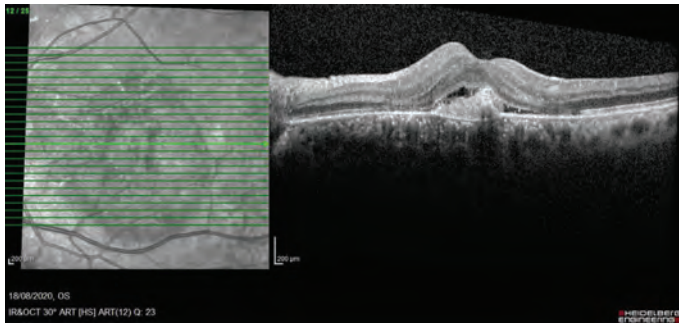

Figure 2. Type 1 CNVM was detected in the left eye of a 59-year-old male patient; the patient was recommended for anti-VEGF therapy
CNVM: Choroidal neovascular membrane, VEGF: Vascular endothelial growth factor

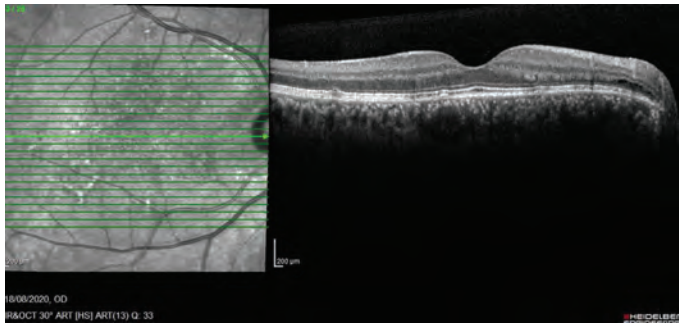

Figure 3. Retinal pigmentary changes were remarkable in the fellow eye of the same patient

To the best of our knowledge, choroidal thickening has not been reported in DM1 patients. The choroid is a very highly vascular tissue that plays an important role in the pathophysiology of many chorioretinal diseases, such as central serous chorioretinopathy (5). Several studies have indicated that choroidal thickness can increase as part of various inflammatory, rheumatologic, metabolic, and systemic diseases (6,7). Metabolic and endocrinologic pathologies are the most reported factors regarding the thickening of the choroid. Kurt et al. (8) reported that the SFCT was higher in inactive Graves disease patients than in a healthy control population. DR and its' effect on choroidal thickness is a well-researched topic. Choi et al. (9) reported on a large series of DR patients in whom treatment-naïve eyes with proliferative or severe non-proliferative DR had thicker choroids than eyes with mild to moderate non-proliferative DR, indicating a relationship between choroidal thickness and the DR stage (9). Additionally, some studies have reported that choroidal thickening decreases in response to diabetic macular edema treatment, such as intravitreal anti-vascular endothelial growth factor (VEGF) agents (10). Diabetes mellitus, insulin resistance,

Table 1. Demographic, clinical, and OCT findings of the study and control groups

	Study group (n=20) (mean ± SD)	Control group (n=29) (mean ± SD)	p value
Age (years)			
Mean	36.4±14.5	38.55±15.3	0.55
Min-max	18-65	17-60	
Gender			
Female	10 (50%)	14 (48%)	0.89
Male	10 (50%)	15 (52%)	
Mean duration of disease (years)	10.8±5.2	-	-
Muscular impairment rating scales			
Grade 1	2 (10%)	-	-
Grade 2	5 (25%)	-	-
Grade 3	5 (25%)	-	-
Grade 4	4 (20%)	-	-
Grade 5	4 (20%)	-	-
OCT finding			
Central macula thickness	275.52±40.31	262.76±9.06	0.09
Subfoveal coroid thickness	341.8±95.04	279.59±46.65	**0.002**
Retinal nerve fiber thickness	103.6±14	101.3±12	0.12

OCT: Optical coherence tomography, SD: Standard deviation, min: Minimum, max: Maximum

and dyslipidemia are common in patients with DM1 due to endocrine involvement (1,2,11). However, the reason for the significantly higher SFCT in our study group remains unclear. Although we did not include patients manifesting with diabetes mellitus, our study participants might have a prediabetic status affecting the SFCT or the choroidal tissue was thickened in DM1 secondary to other metabolic processes than glycemic pathways.

In addition to muscular dystrophy, many systemic findings, such as endocrinological, gastrointestinal, and cardiac systems, can accompany DM1 (11). The most common ocular involvement finding in DM1 is presenile cataract formation at rates of 90% (12). In our study group, the presence of cataracts was detected in only 10% of eyes. The reason for this low cataract rate might be the relatively young age of our study group.

Ptosis, ocular motility disorders, low intraocular pressure, and retinal pigment changes are other ocular abnormalities reported in patients with DM1 (12). Kersten et al. (4) observed signs of high ERM rates in patients with myotonic dystrophy. ERMs are a treatable cause of visual impairment that can lead to reduced best-corrected visual acuity (BCVA) and a reduction in other visual symptoms, such as metamorphosis and micropsy. ERMs are likely to be asymptomatic in DM1 patients because BCVA is affected in stage 2 and later ERM stages. The pathophysiology that causes an increase in ERM in patients with DM1 is unclear. In the general population, ERMs are associated with a variety of ocular abnormalities and systemic diseases, such as intraocular inflammation, retinal vein occlusion, DR, and trauma-causing conditions, including cataract extraction surgery (4,13-16). The reason why we did not detect any ERMs in our DM1 group might be because we included younger patients without diabetes mellitus and excluded pseudophakic eyes.

Kim et al. (17) reported a case with pigmentary retinopathy. In our case series, the CNVM was detected in the left eye and retinal pigmentary changes were observed in the fellow eye of the same patient. Zinkernagel et al. (18) reported a single case of a young DM patient with type 1 CNVM whom they treated with anti-VEGF injections. The presence of type 1 CNVM patient in our cohort was attributed to his older age rather than to DM1.

Posterior subcapsular cataracts were detected in two eyes, but cataract surgery was not planned because of good vision. PAMM was incidentally found in one eye of our patients. This situation was thought to be secondary to a temporary arterial obstruction, as PAMM has not been reported in DM1 patients.

Study Limitations

Our study had some limitations. The small sample size of our study group limited statistical power but DM1 is a rare disease and our study reflects the findings of a single center. We excluded pseudophakic patients to eliminate the possible effect of cataract surgery on the formation of ERM. Our study group consisted of younger DM1 patients compared to the study groups of previous reports and this may have affected the incidence of vitreomacular and retinal disorders in our group.

CONCLUSION

OCT is a readily available, fast, and accurate method to identify retinal pathologies, such as ERMs, even in the presence of cataracts. Additionally, the visual disturbances associated with myotonic dystrophy are not only caused by cataracts but by a variety of retinal disorders. We strongly recommend an OCT examination for DM1 patients as a part of the routine ophthalmologic evaluation. Further prospective studies will be conducted in a larger series of older patients.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for the study from University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital Location Ethics Committee (30.06.2020-277). It was made following the principles of the Declaration of Helsinki.

Informed Consent: Written consent was obtained from the patient for the use of images.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.A., B.E., Concept: O.A., B.E., Design: O.A., B.E., Data Collection or Processing: O.A., B.E., Analysis or Interpretation: O.A., B.E., Literature Search: O.A., B.E., Writing: O.A., B.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Smith CA, Gutmann L. Myotonic Dystrophy Type 1 Management and Therapeutics. Curr Treat Options Neurol 2016;18:52.
2. Thornton CA. Myotonic dystrophy. Neurol Clin 2014;32:705-19.
3. Mathieu J, Boivin H, Meunier D, Gaudreault M, Bégin P. Assessment of a disease-specific muscular impairment rating scale in myotonic dystrophy. Neurology 2001;56:336-40.

4. Kersten HM, Roxburgh RH, Child N, Polkinghorne PJ, Frampton C, Danesh-Meyer HV. Epiretinal membrane: a treatable cause of visual disability in myotonic dystrophy type 1. J Neurol 2014;261:37-44.

5. Gemenetzi M, De Salvo G, Lotery AJ. Central serous chorioretinopathy: an update on pathogenesis and treatment. Eye (Lond) 2010;24:1743-56.

6. Yazgan S, Arpaci D, Celik HU, Dogan M, Isık I. Macular Choroidal Thickness May Be the Earliest Determiner to Detect the Onset of Diabetic Retinopathy in Patients with Prediabetes: A Prospective and Comparative Study. Curr Eye Res 2017;42:1039-47.

7. Bolukbasi S, Erden B, Cakir A, Bayat AH, Elcioglu MN, Yurttaser Ocak S, et al. Pachychoroid Pigment Epitheliopathy and Choroidal Thickness Changes in Coeliac Disease. J Ophthalmol 2019;2019:6924191.

8. Kurt MM, Akpolat C, Evliyaoglu F, Yilmaz M, Ordulu F. Evaluation of Retinal Neurodegeneration and Choroidal Thickness in Patients with Inactive Graves' Ophthalmopathy. Klin Monbl Augenheilkd 2021 Mar 17. English.

9. Choi MG, Chung H, Yoon YH, Kim JT. Effects of Systemic Profiles on Choroidal Thickness in Treatment-Naïve Eyes With Diabetic Retinopathy. Invest Ophthalmol Vis Sci 2020;61:12.

10. Okamoto M, Yamashita M, Ogata N. Effects of intravitreal injection of ranibizumab on choroidal structure and blood flow in eyes with diabetic macular edema. Graefes Arch Clin Exp Ophthalmol 2018;256:885-92.

11. Alsaggaf R, Pfeiffer RM, Wang Y, St George DMM, Zhan M, Wagner KR, et al. Diabetes, metformin and cancer risk in myotonic dystrophy type I. Int J Cancer 2020;147:785-92.

12. Ikeda KS, Iwabe-Marchese C, França MC Jr, Nucci A, Carvalho KM. Myotonic dystrophy type 1: frequency of ophthalmologic findings. Arq Neuropsiquiatr 2016;74:183-8.

13. Kimizuka Y, Kiyosawa M, Tamai M, Takase S. Retinal changes in myotonic dystrophy. Clinical and follow-up evaluation. Retina 1993;13:129-35.

14. Hayasaka S, Kiyosawa M, Katsumata S, Honda M, Takase S, Mizuno K. Ciliary and retinal changes in myotonic dystrophy. Arch Ophthalmol 1984;102:88-93.

15. Ng CH, Cheung N, Wang JJ, Islam AF, Kawasaki R, Meuer SM, et al. Prevalence and risk factors for epiretinal membranes in a multi-ethnic United States population. Ophthalmology 2011;118:694-9.

16. Koh V, Cheung CY, Wong WL, Cheung CM, Wang JJ, Mitchell P, et al. Prevalence and risk factors of epiretinal membrane in Asian Indians. Invest Ophthalmol Vis Sci 2012;53:1018-22.

17. Kim US, Kim JS, Hwang JM. A case of myotonic dystrophy with pigmentary retinal changes. Korean J Ophthalmol 2009;23:121-3.

18. Zinkernagel MS, Hornby SJ, MacLaren RE. Choroidal new vessels in type 1 myotonic dystrophy-related macular dystrophy respond to anti-VEGF therapy. Eye (Lond) 2012;26:1595-6.

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Working in a Pandemic Hospital during COVID-19 Outbreak: Current Conditions and Depression, Anxiety, and Stress Levels

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Abstract

Objective: Healthcare workers (HCW), who actively participate in combating the coronavirus disease-2019 (COVID-19) epidemic, may experience rage and anxiety due to the high performance expected from them. This study aimed to reveal how working in a pandemic hospital affects the psychological status of healthcare professionals.

Methods: 446 HCW, working frontline in a pandemic hospital, were included the study. Questions including basic demographic data and exposure risks to COVID-19 and depression anxiety stress scale (DASS-21) were used as data collection tools. The forms were delivered online, and the responses were similarly collected.

Results: DASS-21 scores of 384 (86.1%) HCW, who had contact with patients diagnosed with COVID-19, were found to be higher than HCW who did not have contact with the patients. When we evaluated the scores of DASS-21, the scores were higher in women ($p<0.01$), HCW diagnosed with COVID-19 among their colleagues ($p<0.01$), and HCW with relatives diagnosed with COVID-19. Anxiety scores of nurses ($p<0.05$) and single HCW, were also high ($p<0.05$).

Conclusion: While the world continues to fight the COVID-19 outbreak, HCW are emotionally affected in this intense process. Providing psychosocial support and intervention to cover all healthcare professionals should be targeted by decision makers.

Keywords: Healthcare worker, COVID-19 outbreak, depression anxiety stress scale

INTRODUCTION

In December 2019, coronavirus disease-2019 (COVID-19) and its newly diagnosed severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) agent, responsible of developing pneumonia, first broke out in Wuhan, China. The clinical spectrum of SARS-CoV-2 infection appears to be wide, encompassing asymptomatic infection, mild upper respiratory tract illness, severe viral pneumonia with respiratory failure, and even death, with many patients being hospitalized with pneumonia in Wuhan (1).

Healthcare workers (HCW) are continually faced by factors such as infectious diseases and exposure to chemical and physical agents. As of 14 February, 2021, 108,153,741 cases were reported related to COVID-19, and 2,579,896 cases were reported in our country on the same date (2). In the 2002 SARS outbreak, 1.725 HCW have been infected. As of 11 February, 2020, 1.716 Chinese HCW was infected with COVID-19. HCW were diagnosed among the first 15 cases (3). As of 10 December, 2020, of 1,100,000 HCW, more than 120,000 were infected with COVID-19, according to the statement of the Turkish Ministry of Health (4).

HCW actively participating in combating the COVID-19 epidemic may be concerned with their families or coworkers contracting the virus or themselves. They may also experience rage, anger, anxiety, and insomnia due to the high performance expected from them (5). Being isolated, working in high-risk areas, and being in direct contact with infected people are common causes

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of trauma (6,7). Widespread media coverage of the clinical course and mortality rate of the outbreak intensifies the personal risk. Working in a high temperature with two layers of protection and masks during long working hours increases the stress. Moreover, behaviors such as not eating or drinking to prevent being infected and not being able to go to the toilet during the busy working hours make the process difficult for HCW. These conditions exhaust the staff both physically and psychologically and cause increased stress (8). Work-related tension and exposure to high stress could cause physical, behavioral, emotional, and psychological problems, which can lead to chronic diseases (9). Work stress is defined as a situation that causes inadequacy in the abilities of the individual and creates tension on both the physical and psychological levels, which can lead to physiological depression and anxiety, headache, muscle tension, insomnia, and lack of attention. Stress and altered hormonal activity can cause a vicious cycle of insomnia. This vicious cycle was experienced during the SARS outbreak, and an improvement in the sleep cycles of the employees was observed only two weeks after the end of the crisis (8,9).

Ensuring the safety, fulfillment, and support of HCW is important during an outbreak to protect them from depression, anxiety, and stress, which were manifested during the COVID-19 outbreak. Regarding COVID-19, it is important to identify the operations and situations that pose a risk to the employees, determine the processes that need to be improved, find solutions, and immediately implement the regulations and measures for the identified risks to provide the best health service and protect the health of HCW, who work devotedly, and their families.

METHODS

University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital is a tertiary training and research hospital in Istanbul, which is the most populous city in Turkey. Our hospital's healthcare professionals work devotedly to serve this population. This is a prospective study, which included 446 HCW working in the frontline between May and September in our hospital. All individuals consented to participate in the study. A power analysis was performed to obtain meaningful results for our study. Out of 1.083 HCW working in the frontline, 383 were included in the study. A form consisting of questions on basic demographic data and direct and indirect exposure risks to COVID-19 and depression anxiety stress scale (DASS-21) were used as data collection tools (10). The data collection tools were prepared via Google forms. They were delivered to healthcare professionals online, and the answers were collected in the same way. All subjects gave consent prior to registration. Two options are given on the informed consent page (yes/no). Subjects who selected "yes" were included in the study. We asked questions on basic demographic data and direct and indirect exposure risks to COVID-19 in Supplement 1 and used the DASS in Supplement 2.

DASS-21 was created by Lovibond and Lovibond, which is the shorter version of DASS-42 (11). The psychometric properties of the Turkish version of DASS-21 in normal and clinical samples were introduced by Saricam (12). In the normal sample, the test-retest correlation coefficients (r) were 0.68 for the depression subscale, 0.66 for the anxiety subscale, and 0.61 for the stress subscale. This scale is a 4-point Likert-type scale and consists of seven questions that measure "depression, stress, and anxiety dimensions". If the individual has five points or more from the depression subdimension, four points or more from the anxiety, and eight points or more from the stress, this indicates that he/she has a relevant problem.

The Ethics Committee of the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, approved the questionnaire and methodology for this study (approval number: 2020/145). The authors assert that all procedures contributing to this work comply with the ethical standards of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital and the Helsinki Declaration of 1975, as revised in 2008. The participants' consent to participate in the study was requested personally from each individual.

Statistical Analysis

Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) program was used for the statistical analysis. Besides comparing descriptive statistical methods (mean, standard deviation, median, frequency, rate, minimum, and maximum), Mann-Whitney U test was used for two groups of variables, which were non-normally distributed, to compare quantitative data. Kruskal-Wallis test was used for comparing three or more groups, which were non-normally distributed, and Dunn-Bonferroni test was used to determine the group that caused the difference. Spearman's correlation analysis was used to evaluate the relationships between quantitative variables. A p value less than 0.05 was considered statistically significant.

RESULTS

Our study included 446 people: 70.9% (n=316) women and 29.1% (n=130) men, working at University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital. The mean age was 32.7±8.65, with an age range between 20

and 64 years. It was observed that 24.9% of the participants were physicians; 39.7%, nurses; 35.4%, other professions (Table 1).

Regarding the direct and indirect COVID-19 exposure risks, it was observed that 58.1% of the subjects worked over 40 hours during the COVID-19 outbreak. 86.1% (n=384) of the participants were in contact with patients diagnosed with COVID-19. 79.2% (n=304) of the participants, who were in contact with patients diagnosed with COVID-19, stated that the patients wore a surgical mask during contact. 88.8% (n=396) of HCW participating in the study stated that, among their colleagues, 37.2% (n=166) were diagnosed with COVID-19 in acquaintance out of workplace (Table 2).

During the COVID-19 outbreak, 40.1% of the subjects' units were changed. Changes in the assigned units were in the ER, 12.8% (n=23), intensive care unit, 29.1% (n=52), inpatient clinic, 42.5% (n=76), operating room, 0.6% (n=1), and outpatient clinic, 15.1% (n=27) (Table 2).

The distribution of the answers given by the healthcare professionals who participated in the study to the questions of DASS-21 are shown in Table 3.

On evaluating the DASS-21 scores according to the descriptive features (Table 4), the DASS-21 scores of the women HCW were significantly higher than men (p=0.008; p=0.001; p=0.001; p<0.01). The anxiety score of single HCW was statistically significantly higher than the married ones (p=0.013; p<0.05).

Table1. Distribution of descriptive properties

n=446		n	%
Age (years)	Avg. ± SD	32.76±8.65	
	Min-max (med.)	20-64 (30)	
Sex	Female	316	70.9
	Male	130	29.1
Marital status	Single	242	54.3
	Married	204	45.7
Partner's profession (n=204)	Healthcare professional	69	33.8
	Not a healthcare professional	114	55.9
	Unemployed	21	10.3
People responsible for taking care (n=404)	No	173	42.8
	Yes	231	57.2
Place to stay after work	Home	357	80.0
	Where I set up with my own means	50	11.3
	Where the institution arranges	39	8.7
Profession	Physician	111	24.9
	Nurse	177	39.7
	Other	158	35.4
Education level	Attending physician	55	12.2
	Physician assistant	56	12.3
	Graduate	44	10.1
	Undergraduate	160	35.9
	Associate degree	90	20.3
	High school	41	9.2

SD: Standard deviation, Min: Minimum, Max: Maximum, Med.: Median, Avg.: Average

Table 2. Distribution of COVID-19 exposure

n=446		n	%
Working experience Med. ± SD; 9.76±9.25	1-5 years	220	49.3
	6-10 years	64	14.3
	11-20 years	93	20.9
	≥21 years	69	15.5
Weekly working hours (hr) Avg. ± SD; 45.92±6.70	≤40 hours	187	41.9
	>40 hours	259	58.1
Assigned unit before pandemic	Emergency room	64	14.3
	Intensive care unit	38	8.5
	Inpatient services	92	20.6
	Operating room	127	28.5
	Outpatient units	125	28.0
Change of unit during pandemic	Yes	179	40.1
	No	267	59.9
Assigned unit (n=179)	Emergency room	23	12.8
	Intensive care unit	52	29.1
	Inpatient services	76	42.5
	Operating room	1	0.6
	Outpatient units	27	15.1
Contact with COVID-19 patient	Yes	384	86.1
	No	62	13.9
Contact with mask wearing COVID-19 patient (n=384)	Yes	304	79.2
	No	80	20.8
Colleagues diagnosed with COVID-19	Yes	396	88.8
	No	50	11.2
Acquaintances diagnosed with COVID-19 outside work place	Yes	166	37.2
	No	280	62.8
Chronic disease	Yes	80	17.9
	No	366	82.1
Psychological support request	Yes	30	6.7
	No	416	93.3

Med.: Median, SD: Standard deviation, COVID-19: Coronavirus disease-2019, Avg.: Average

There was a statistically significant difference among the anxiety and stress scores of the hospital staff according to their professional status (p=0.023; p<0.05; p=0.004; p<0.01). According to the results of the dual comparison performed to determine the difference, the anxiety score of participating nurses was significantly higher than those in other professions (p=0.023; p<0.05). The stress score of participating physicians or nurses was significantly higher than those in other professions (p=0.030; p=0.007; p<0.05) (Table 4).

On evaluating COVID-19 exposure risk and DASS-21 scores (Table 5), DASS-21 scores of the coworkers diagnosed with COVID-19 were statistically significantly higher than colleagues not diagnosed with COVID-19 (p=0.001; p<0.01).

DASS-21 scores of HCW with any relatives diagnosed with COVID-19 outside of the workplace were statistically significantly higher than those with relatives not diagnosed with COVID-19 (p=0.008; p<0.01; p=0.025; p<0.05; p=0.025; p<0.05) (Table 5).

The depression and stress scores of HCW working over 40 hours per week were statistically significantly higher than those working less than 40 hours per week (p=0.003, p<0.01; p=0.024, p<0.05, respectively) (Table 5).

During the COVID-19 outbreak, the depression, anxiety, and stress scores of HCW who had a change in their units were statistically significantly higher than those experiencing no changes (p=0.007, p<0.01; p=0.034, p<0.05; p=0.001, p<0.01, respectively) (Table 5).

DISCUSSION

HCW experience significant stress during infectious outbreaks. COVID-19 is a worldwide major public health problem, which is complex, infectious, and often sensitive. It brings significant difficulties regarding social prevention, control, and pre-pure therapy. Moreover, reports on the psychological impact of SARS on HCW have shown that high levels of distress are common (7).

Table 3. Distribution of the answers given to the depression, anxiety, and stress scale questions

	None of the time		Some of the time		Most of the time		All of the time	
	n	%	n	%	n	%	n	%
I found it difficult to relax	65.0	14.6	205.0	46.0	131.0	29.4	45.0	10.0
I was aware of dryness of my mouth	118.0	26.5	202.0	45.3	96.0	21.5	30.0	6.7
I couldn't seem to experience any positive feeling at all	104.0	23.3	219.0	49.1	86.0	19.3	37.0	8.3
I experienced breathing difficulty (e.g., excessively rapid breathing, breathlessness in the absence of physical exertion)	166.0	37.2	193.0	43.3	64.0	14.3	23.0	5.2
I had a hard time taking the first step required to do a job	150.0	33.6	197.0	44.2	78.0	17.5	21.0	4.7
I tended to over-react to situations	138.0	30.9	175.0	39.2	107.0	24.0	26.0	5.8
I experienced trembling (e.g., in the hands)	266.0	59.6	122.0	27.4	51.0	11.4	7.0	1.6
I felt that I was using a lot of nervous energy	138.0	30.9	176.0	39.5	103.0	23.1	29.0	6.5
I was worried about situations in which I might panic and make a fool of myself	227.0	50.9	144.0	32.3	53.0	11.9	22.0	4.9
I had the feeling that I had no expectations	161.0	36.1	161.0	36.1	87.0	19.5	37.0	8.3
I found that I was very irritable	245.0	54.9	118.0	26.5	56.0	12.6	27.0	6.1
It was hard to relax and release myself	116.0	26.0	189.0	42.4	100.0	22.4	41.0	9.2
I felt sad and depressed	140.0	31.4	185.0	41.5	85.0	19.1	36.0	8.1
I was intolerant of anything that kept me from getting on with what I was doing	170.0	38.1	178.0	39.9	68.0	15.2	30.0	6.7
I felt I was close to panic	175.0	39.2	171.0	38.3	78.0	17.5	22.0	4.9
I was unable to become enthusiastic about anything	147.0	33.0	176.0	39.5	88.0	19.7	35.0	7.8
I felt I was pretty worthless	189.0	42.4	139.0	31.2	65.0	14.6	53.0	11.9
I felt that I was rather touchy	157.0	35.2	169.0	37.9	91.0	20.4	29.0	6.5
I was aware of the action of my heart in the absence of physical exertion (e.g., sense of heart rate increase, heart missing a beat)	144.0	32.3	187.0	41.9	80.0	17.9	35.0	7.8
I felt scared without any good reason	160.0	35.9	170.0	38.1	82.0	18.4	34.0	7.6
I felt that life wasn't worthwhile	155.0	34.8	167.0	37.4	80.0	17.9	44.0	9.9

Table 4. Evaluation of depression, anxiety, and stress scale scores according to descriptive features					
			Depression	**Anxiety**	**Stress**
Age (years)		**r[a]**	-0.020	-0.061	-0.050
		p	**0.678**	**0.201**	**0.288**
Sex	**Female (n=316)**	Min-max (med.)	0-21 (7)	0-20 (6)	0-21 (7)
		Avg. ± SD	7.52±5.14	6.63±4.56	7.71±4.89
	Male (n=130)	Min-max (med.)	0-21 (6)	0-21 (4)	0-21 (5)
		Avg. ± SD	6.12±4.97	4.78±4.46	5.9±4.9
		Test value	Z: -2.645	Z: -4.410	Z: -3.739
		p	**[b]0.008****	**[b]0.001****	**[b]0.001****
Marital status	**Single (n=242)**	Min-max (med.)	0-21 (7)	0-21 (5)	0-21 (7)
		Avg. ± sd	7.65±5.74	6.65±4.87	7.64±5.23
	Married (n=204)	Min-max (med.)	0-19 (6)	0-18 (5)	0-21 (7)
		Avg. ± SD	6.47±4.21	5.43±4.17	6.64±4.57
		Test value	Z: -1.538	Z: -2.472	Z: -1.757
		p	**[b]0.124**	**[b]0.013***	**[b]0.079**
Partner's profession (n=204)	**Healthcare professional (n=69)**	Min-max (med.)	0-18 (6)	0-15 (5)	0-16 (7)
		Avg. ± sd	6.43±4	5.24±3.81	6.75±4.14
	Not a healthcare professional (n=114)	Min-max (med.)	0-19 (7)	0-18 (6)	0-21 (7)
		Avg. ± SD	6.74±4.45	5.97±4.44	7.09±4.86
	Unemployed (n=21)	Min-max (med.)	0-13 (5)	0-12 (2)	0-13 (3)
		Avg. ± SD	5.19±3.97	3.57±3.61	4.33±4.05
		Test value	χ^2: 2.271	χ^2: 6.641	χ^2: 6.676
		p	**[c]0.321**	**[c]0.036***	**[c]0.036***
People responsible for taking care (n = 404)	**No (n=173)**	Min-max (med.)	0-21 (6)	0-20 (5)	0-21 (6)
		Avg. ± SD	7.13±5.44	6.09±4.76	6.96±5.07
	Yes (n=231)	Min-max (med.)	0-21 (7)	0-21 (6)	0-21 (7)
		Avg ± SD	7.02±4.94	5.97±4.51	7.27±4.9
		Test value	Z: -0.120	Z: -0.074	Z: -0.757
		p	**[b]0.904**	**[b]0.941**	**[b]0.449**
Place to stay after work	**Home (n=357)**	Min-max (med.)	0-21 (7)	0-21 (5)	0-21 (7)
		Avg. ± SD	7.17±5.15	6.1±4.64	7.2±5.03
	Where I set up with my own means (n=50)	Min-max (med.)	0-21 (6)	0-17 (5)	0-19 (7)
		Avg. ± SD	6.96±5.28	6.08±4.62	7.1±4.8
	Where the institution arranges (n=39)	Min-max (med.)	0-18 (7)	0-14 (6)	0-16 (7)
		Avg. ± SD	6.77±4.79	5.97±4.3	7.1±4.62
		Test value	χ^2: 0.179	χ^2: 0.013	χ^2: 0.044
		p	**[c]0.915**	**[c]0.994**	**[c]0.978**
Profession	**Physician (n=111)**	Min-max (med.)	0-21 (7)	0–19 (5)	0–20 (7)
		Avg. ± SD	7.53±5.26	5.84±4.52	7.63±4.98
	Nurse (n 177)	Min-max (med.)	0-21 (7)	0-20 (6)	0-21 (7)
		Avg. ± SD	7.36±4.91	6.69±4.5	7.74±4.76
	Other (n=158)	Min-max (med.)	0-21 (6)	0-21 (5)	0-21 (5)
		Avg. ± SD	6.54±5.25	5.59±4.72	6.24±5.05
		Test value	χ^2: 3.951	χ^2: 7.513	χ^2: 11.033
		p	**[c]0.139**	**[c]0.023***	**[c]0.004****

Table 4. Continued					
			Depression	**Anxiety**	**Stress**
Chronic disease	**Yes (n=80)**	Min-max (med.)	0-21 (7)	0-21 (6)	0-21 (7)
		Avg. ± SD	7.81±5.34	7.24±4.84	8.1±5.52
	No (n=366)	Min-max (med.)	0-21 (6)	0-20 (5)	0-21 (7)
		Avg. ± SD	6.96±5.07	5.84±4.52	6.98±4.81
		Test value	Z: -1.257	Z: -2.478	Z: -1.406
		p	[b]**0.209**	[b]**0.013***	[b]**0.160**
Psychological support request	**Yes (n=30)**	Min-max (med.)	1-21 (8.5)	0-21 (8)	1-21 (9.5)
		Avg. ± SD	10.2±5.59	9.63±5.46	10.9±5.25
	No (n=416)	Min-max (med.)	0-21 (6)	0-20 (5)	0-21 (7)
		Avg. ± SD	6.89±5.03	5.83±4.43	6.91±4.83
		Test value	Z: -3.157	Z: -3.884	Z: -3.930
		p	[b]**0.002****	[b]**0.001****	[b]**0.001****

[a]r: Spearman's correlation coefficient, [b]Mann-Whitney U test, [c]Kruskal-Wallis test, *p<0.05, **p<0.01, Med.: Median, SD: Standard deviation, Avg.: Average

Table 5. Evaluation of depression, anxiety, and depression scale scores regarding COVID-19 exposure					
			Depression	**Anxiety**	**Stress**
Working experience	**1-5 years (n=220)**	Min-max (med.)	0-21 (7)	0-21 (5)	0-21 (7)
		Avg. ± SD	7.55±5.51	6.5±4.84	7.65±5.13
	6-10 years (n=64)	Min-max (med.)	0-21 (5.5)	0-18 (5)	0-19 (5)
		Avg. ± SD	6.84±5.36	5.33±4.48	6.23±5.1
	11-20 years (n=93)	Min-max (med.)	0-21 (7)	0-20 (6)	0-21 (7)
		Avg. ± SD	6.74±4.41	5.87±4.06	7.04±4.42
	≥21 years (n=69)	Min-max (med.)	0-19 (6)	0-18 (5)	0-21 (7)
		Avg. ± SD	6.46±4.46	5.78±4.57	6.77±4.87
		Test value	χ^2: 1.965	χ^2: 3.646	χ^2: 5.272
		p	[c]**0.580**	[c]**0.302**	[c]**0.153**
Weekly working hours	**≤40 hours (n=187)**	Min-max (med.)	0–21 (5)	0-21 (5)	0-21 (6)
		Avg. ± SD	6.29±4.83	5.72±4.64	6.59±4.82
	>40 hours (n=259)	Min-max (med.)	0-21 (7)	0-20 (6)	0-21 (7)
		Avg. ± SD	7.7±5.26	6.36±4.56	7.61±5.02
		Test value	Z: -2.999	Z: -1.775	Z: -2.256
		p	[b]**0.003****	[b]**0.076**	[b]**0.024***
Change of unit during pandemic	**Yes (n=179)**	Min-max (med.)	0-21 (7)	0-20 (6)	0-21 (7)
		Avg. ± SD	7.72±4.9	6.41±4.66	7.59±4.97
	No (n=267)	Min-max (med.)	0-21 (6)	0-21 (5)	0-21 (7)
		Avg. ± SD	6.7±5.24	5.87±4.56	6.91±4.94
		Test value	Z: -2.681	Z: -1.344	Z: -1.592
		p	[b]**0.007****	[b]**0.179**	[b]**0.111**
Assigned unit (n=179)	**Emergency room (n=23)**	Min-max (med.)	0-18 (7)	0-13 (5)	0-17 (7)
		Avg. ± SD	7.35±5.36	5.96±4.11	7.65±4.78
	Intensive care unit (n=52)	Min-max (med.)	0-21 (7,5)	0-20 (6)	0-21 (7)
		Avg. ± SD	8.52±5.4	6.9±5.16	7.94±5.18
	Inpatient services (n=76)	Min-max (med.)	0-21 (7)	0-19 (6)	0-20 (7.5)
		Avg.± SD	7.54±4.66	6.29±4.57	7.61±4.91

Table 5. Continued					
			Depression	**Anxiety**	**Stress**
Assigned unit (n=179)	**Operating room (n=1)**	Min-max (med.)	12	12	13
		Avg.± SD	12	12	13
	Outpatient unit (n=27)	Min-max (med.)	0-18 (7)	0-15 (6)	0-16 (8)
		Avg. ± SD	6.85±4.16	6±4.42	6.59±4.98
		Test value	χ^2: 0.878	χ^2: 0.393	χ^2: 0.795
		p	[c]**0.831**	[c]**0.942**	[c]**0.851**
Contact with COVID-19 patient	**Yes (n=384)**	Min-max (med.)	0-21 (7)	0-21 (5)	0-21 (7)
		Avg. ± SD	7.24±5.1	6.24±4.57	7.44±4.95
	No (n=62)	Min-max (med.)	0-21 (6)	0-19 (4)	0-21 (5)
		Avg. ± SD	6.31±5.25	5.13±4.75	5.6±4.71
		Test value	Z: -1.496	Z: -2.119	Z: -2.826
		p	[b]**0.135**	[b]**0.034***	[b]**0.005****
Contact with mask wearing COVID-19 patient (n=384)	**Yes (n=304)**	Min-max (med.)	0-21 (6)	0-21 (5)	0-21 (7)
		Avg. ± SD	7.03 ± 5.08	6.08±4.53	7.21±4.93
	No (n=80)	Min-max (med.)	0–21 (7.5)	0-19 (6.5)	0-20 (8)
		Avg. ± SD	8.03 ± 5.13	6.89±4.67	8.31±4.99
		Test value	Z: −1.758	Z: -1.446	Z: -1.808
		p	[b]**0.079**	[b]**0.148**	[b]**0.071**
Colleagues diagnosed with COVID-19	**Yes (n=396)**	Min-max (med.)	0–21 (7)	0-21 (6)	0-21 (7)
		Avg. ± SD	7.41 ± 5.07	6.34±4.6	7.55±4.93
	No (n=50)	Min-max (med.)	0–21 (3.5)	0-19 (3)	0-19 (4)
		Avg. ± SD	4.7 ± 4.95	4.12±4.2	4.3±4.17
		Test value	Z: −3.991	Z: -3.683	Z: -4.657
		p	[b]**0.001****	[b]**0.001****	[b]**0.001****
Acquaintances diagnosed with COVID-19 outside work place	**Yes (n=166)**	Min-max (med.)	0–21 (7)	0-21 (6)	0-21 (7)
		Avg. ± SD	7.91 ± 5.18	6.75±4.82	8.08±5
	No (n=280)	Min-max (med.)	0–21 (6)	0-19 (5)	0-21 (7)
		Avg. ± SD	6.64 ± 5.05	5.7±4.43	6.65±4.86
		Test value	Z: −2.647	Z: -2.236	Z: -2.955
		p	[b]**0.008****	[b]**0.025***	[b]**0.003****

[b]Mann-Whitney U test, Kruskal-Wallis test, *p<0.05, **p<0.0, Med.: Median, SD: Standard deviation, COVID-19: Coronavirus disease-2019, Avg.: Average

Many HCW were emotionally affected during the SARS outbreak. Therefore, it is very important for health institutions to provide psychosocial support and intervention to HCW during outbreaks (13). Understanding the psychological impact of the COVID-19 outbreak among HCW will guide us to take the necessary measures and plan improvements.

Of the 446 HCW participating in our study, 70.9% were women, and DASS-21 scores in women were significantly higher than men. In terms of profession, 24.9% of the participants were physicians, and 39.7% were nurses. The anxiety scores of the participating nurses and stress scores of participating physicians and nurses were higher than other occupational groups. The anxiety score of single HCW was also higher than married one. Similar to our study, the study investigating the psychological impact of the SARS outbreak in 2003 on HCW in Singapore reported that single HCW were at higher risk than married ones. It has been reported that single HCW are 1.4 times more likely to experience psychiatric symptoms than married ones (13). In a study including 469 HCW during the H1N1 pandemic, nurses were also shown to be more worried than other healthcare staff (14). In numerous studies conducted in the UK, 28-32% of the doctors and nurses achieved a score above the "emotional distress" threshold in the 12-Item General Health Questionnaire (15-17).

Long weekly working hours can cause an increase in stress related to COVID-19 infection, caused by respiratory droplets and close contact transmission. Ran Li et al. showed that significant COVID-19 infection rates were detected connected to the daily working hours. Depending on the risks of the workplaces of HCW, it is recommended that the hours of duty be limited to less than 10 hours a day (3). HCW in China have long working hours, exceeding an average of 54 hours per week (18). In our study, it was observed that 58.1% of the HCW worked over 40 hours. Depression and stress scores of HCW working more than 40 hours a week were higher compared with those working 40 hours a week or less. Long working hours will probably increase the risk of infection for HCW, while moderate working hours will benefit the employee's safety. It can be said that long working hours increase the risk of infection in employees, as well as causing psychological effects, which may be associated with fear of infection.

In our study, the stress, depression, and anxiety scores of 384 (86.1%) HCW, who were in contact with patients diagnosed with COVID-19, were higher than HCW who were not in contact with the patients. In a study including 1257 HCW working in the clinic of COVID-19 patients in 34 hospitals in China, it was reported that the symptoms of depression, anxiety, and distress in nurses, women, and frontline HCW were more severe than other HCW (19). In a study examining traumatization in teams that helped control COVID-19, nurses who were in close contact with patients diagnosed with COVID-19 and who were directly exposed to their physical and psychological cases were prone to traumatization (20). In another study conducted during the COVID-19 outbreak, the prevalence of stress related insomnia among HCW was 36.1%, and during the SARS outbreak, it was 34.2% in Hong Kong and 37% in Taiwan (8). Similar to the results of our study, in a study conducted in Singapore including HCW who also worked hard during the epidemic, 68 participants (14.5%) were found positive for anxiety, 42 (8.9%) for depression, and 31 (6.6%) for stress (21). During the H1N1 influenza pandemic, a study including HCW reported that 56.7% of HCW were worried about the pandemic and their anxiety levels were moderately high, and 20.7% presented scores that indicated mild-to-moderate psychological distress (14). For this reason, precautions should be taken against the psychological problems that may occur in HCW who participate actively in the pandemic process.

88.8% of HCW, who participated in our study, were diagnosed with COVID-19 among their colleagues. In our hospital, which serves as a pandemic hospital, 343 HCW were diagnosed with COVID-19 between 15 March and 30 August. China reported that, by February 25, 2020, 3387 infected HCW were in Hubei only, of which at least 18 died (22). As HCW participate actively in the treatment and care of patients during a pandemic, the risks of contracting the disease increase. This affects the psychology of HCW.

37.2% of the participants stated they have relatives who have been diagnosed with COVID-19, outside their workplace. Anxiety, depression, and stress scores of HCW with any relatives diagnosed with COVID-19, outside the workplace, were found to be statistically significantly higher than those without. During the H1N1 pandemic, very few HCW (6.6%) restricted their social contact, and fewer (3.8%) were isolated by family members and friends for working in the hospital. However, the degree of anxiety was significantly associated with the restriction of social contacts (14). We think that HCW's fear of infecting their families and therefore being isolated from them can increase their stress.

Study Limitations

Our study has limitations. Data obtained from self-reported answers were not verified against medical records. Performing similar studies with larger samples on how to protect HCW will provide significant benefits to the public health. We hope that our findings will contribute to the work of psychological studies and support strategies that can minimize the psychological impact, anxiety, depression, and stress during the COVID-19 pandemic.

CONCLUSION

The pandemic process affects HCW even more with the exposure to patients diagnosed with COVID-19. Psychological support programs should be planned, and psychosocial support and intervention should cover all HCW. Identifying mental health problems such as depression, anxiety, and stress and the factors affecting them will enable developing appropriate screening and intervention programs for HCW. With the improvements and interventions, HCW can go through this intense process with minimal damage.

Ethics

Ethics Committee Approval: The Ethics Committee of the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, approved the questionnaire and methodology for this study (approval number: 2020/145).

Informed Consent: The participants' consent to participate in the study was requested personally from each individual.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.P., F.C., Design: Ö.P., F.C., Data collection or Processing: Ö.P., F.C., Analysis or Interpretation: Ö.P., Literature Search: Ö.P., F.C., Writing: Ö.P., F.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
2. WHO Coronavirus (COVID-19) Disease Dashboard. Available from: https://covid19.who.int/ Accessed on 25.06.2020.
3. Ran L, Chen X, Wang Y, Wu W, Zhang L, Tan X. Risk Factors of Healthcare Workers With Coronavirus Disease 2019: A Retrospective Cohort Study in a Designated Hospital of Wuhan in China. Clinical Infectious Diseases 2020;71:2218-21.
4. Turkish Ministry of Health information meeting. Available at: https://tr.euronews.com/saglık-bakan-koca-covid-19-la-mucadelede-gelinen-son-noktay-degerlendiriyor. Accessed on 03.06.2020.
5. Centers for Disease Control and Prevention (CDC). Severe acute respiratory syndrome--Taiwan, 2003. MMWR Morb Mortal Wkly Rep 2003;52:461-6.
6. Wu P, Fang Y, Guan Z, Fan B, Kong J, Yao Z, et al. The psychological impact of the SARS epidemic on hospital employees in China: exposure, risk perception, and altruistic acceptance of risk. Can J Psychiatry 2009;54:302-11.
7. Maunder RG, Lancee WJ, Rourke S, Hunter JJ, Goldbloom D, Balderson K, et al. Factors associated with the psychological impact of severe acute respiratory syndrome on nurses and other hospital workers in Toronto. Psychosom Med 2004;66:938-42.
8. Zhang C, Yang L, Liu S, Ma S, Wang Y, Cai Z, et al. Survey of Insomnia and Related Social Psychological Factors Among Medical Staff Involved in the 2019 Novel Coronavirus Disease Outbreak. Front Psychiatry 2020;11:306.
9. Clegg A. Occupational stress in nursing: a review of the literature. J Nurs Manag 2001;9:101-6.
10. Lovibond SH, Lovibond PF. Manual for the Depression Anxiety Stress Scales, (2nd ed.). Sydney, Australia: Pychology Foundation of Australia,1995.
11. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behav Res Ther 1995;33:335-43.
12. Sarıçam H. The Psychometric Properties of Turkish Version of Depression Anxiety Stress Scale-21 (DASS-21) in Community and Clinical Samples. JCBPR 2018;7:19-30.
13. Chan AO, Huak CY. Psychological impact of the 2003 severe acute respiratory syndrome outbreak on health care workers in a medium size regional general hospital in Singapore. Occup Med (Lond) 2004;54:190-6.
14. Goulia P, Mantas C, Dimitroula D, Mantis D, Hyphantis T. General hospital staff worries, perceived sufficiency of information and associated psychological distress during the A/H1N1 influenza pandemic. BMC Infect Dis 2010;10:322.
15. Firth-Cozens J. Emotional distress in junior house officers. Br Med J (Clin Res Ed) 1987;295:533-6.
16. Ramirez AJ, Graham J, Richards MA, Cull A, Gregory WM, Leaning MS, et al. Burnout and psychiatric disorder among cancer clinicians. Br J Cancer 1995;71:1263-9.
17. Hetherington A. The Exent and Source of Stress in Emergency Care. Report no: 9110,1993, UK, Cranfield University.
18. Wen J, Hao T, Hu X. Doctor's Workload in China: A Status-quo Study. Chin J Evid-Based Med 2015;15:133-6.
19. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors Associated With Mental Health Outcomes Among Health Care Workers Exposed to Coronavirus Disease 2019. JAMA Netw Open 2020;3:e203976.
20. Li Z, Ge J, Yang M, Feng J, Qiao M, Jiang R, et al. Vicarious traumatization in the general public, members, and non-members of medical teams aiding in COVID-19 control. Brain Behav Immun 2020;88:916-9.
21. Tan BYQ, Chew NWS, Lee GKH, Jing M, Goh Y, Yeo LLL, et al. Psychological Impact of the COVID-19 Pandemic on Health Care Workers in Singapore. Ann Intern Med 2020;173:317-20.
22. Schwartz J, King CC, Yen MY. Protecting Healthcare Workers During the Coronavirus Disease 2019 (COVID-19) Outbreak: Lessons From Taiwan's Severe Acute Respiratory Syndrome Response. Clin Infect Dis 2020;71:858-60.

CASE REPORT

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Using a Dermis Fat Graft for Volumetric Rejuvenation of Deep Superior Sulcus in the Eyelid Due to an Anophthalmic Socket

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Abstract

Enophthalmos, shallow fornices, and deep superior sulci in the eyelids may be encountered in patients with an anophthalmic socket due to gradual fibrosis of orbital tissues. Herein, a 42-year-old woman presented to our clinic due to dissatisfaction with the sunken appearance of her right upper eyelid. She had undergone evisceration surgery in the past and had been using a prosthesis in the right eye for the last 30 years. Moreover, ophthalmologic examination revealed a deep superior sulcus deformity of the right eyelid. A dermis fat graft was placed and volumetric correction of the right upper eyelid sulcus deformity was performed, which resulted in significant rejuvenation of the upper eyelid sulcus deformity on postoperative follow-up. In conclusion, dermis fat grafts can be used as a safe alternative method for volumetric correction of intraconal or extraconal volume loss that develops in patients with an anophthalmic socket.

Keywords: Anophthalmic socket, dermis fat graft, periorbital rejuvenation, deep superior sulcus, sunken eyelid

INTRODUCTION

Patients with an anophthalmic socket may develop enophthalmos, shallow fornices, and deep upper eyelid sulci due to gradual fibrosis of orbital tissues (1). As a result, dermis fat grafts have been utilized to correct enophthalmos and repair eyelid volume loss (2-7). The usage of dermis fat grafts is especially significant in patients with an anophthalmic socket, since deep upper eyelid sulcus deformities can negatively impact their appearance, causing cosmetic concerns. Therefore, in this case report, we present the surgical repair of a deep sulcus deformity in the upper eyelid due to an anophthalmic socket using dermis fat grafting.

CASE PRESENTATION

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. This case report follows the ethical principles outlined in the Declaration of Helsinki.

A 42-year-old woman presented to our clinic due to dissatisfaction with the sunken appearance of her right upper eyelid. She had a previous history of evisceration surgery and had been using an ocular prosthesis for 30 years since then. Ophthalmologic examination revealed a deep sulcus deformity of the right upper eyelid (Figure 1a). There was an implant in the orbit, and no pathology was observed in the anophthalmic socket. Thus, she was recommended rejuvenation of the upper eyelid sulcus deformity using a dermis fat graft. Under general anesthesia, the upper eyelid crease was marked using a sterile marking pen. Then, 3 cc of a local anesthetic solution (2% lidocaine with 1:100,000 epinephrine, diluted half with saline) was injected along the eyelid crease. Next, a skin incision in the upper eyelid crease was made using a Westcott scissor,and the orbicularis muscle and orbital septum were opened (Figure 1b). Afterward, the preaponeurotic fat was identified and exposed. The periosteum overlaying the superior orbital rim was dissected, and the atrophic area in the superior-nasal and superior-temporal orbital regions was observed (Figure 1c).

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The horizontal size of the eyelid skin incision was measured. Then, the superolateral quadrant of the gluteal region was marked using the marking pen. Approximately 2 cc of the local anesthetic solution (2% lidocaine with 1:100,000 epinephrine, diluted half with saline) was injected, and a 2×1×0.5 cm dermis fat graft was harvested from the gluteal region (Figure 1d, 2a). Since postoperative atrophy can be observed in the dermis fat graft, the graft harvested was roughly 30% larger than the orbital defect. The size of the harvested graft can vary depending on the surgeon's preference (7). The donor site was then repaired with primary closure using 3-0 polyglactin sutures. The epidermal layer of the harvested graft was excised in order to ensure better vascularization of the graft in the recipient bed and to prevent possible cyst formation.

Following excision, the dermis fat graft was placed in the atrophic area, with the dermis part facing anteriorly and the fat part posteriorly (Figure 2b). The superior border of the dermis fat graft was anchored in place to the superior orbital rim using 6-0 polyglactin sutures. The graft was then trimmed to fit the available space, and the superior sulcus deformity was observed to significantly improve (Figure 2c). Then, the upper eyelid crease was reformed using 6-0 polyglactin sutures and the skin incision was closed. Follow-up examination on postoperative day 10 showed further significant improvement of the upper eyelid sulcus deformity (Figure 2d).

DISCUSSION

An optimum anophthalmic socket is required for ideal positioning of an ocular prosthesis. Anophthalmic sockets can develop various complications, including discharge, infection, entropion, ectropion, conjunctival cysts, orbital implant exposure or extrusion, orbital implant migration, contracted socket, and ptosis (1-9). Moreover, the mechanical impact of the prosthetic eye can lead to gradual volume loss in orbital tissues, which affects the positioning of a prosthesis and consequently increases the risk of complications (1).

In ophthalmology, volume augmentation in the anophthalmic socket is among the most common areas of use for dermis fat grafts (1-5). These grafts, in particular, can be used to repair volume deficits in the upper and lower eyelids. While they can be placed in the intraconal space, they can also be preferred for enophthalmos that may occur after orbital fracture repair (1-5). Additionally, these grafts can increase cosmetic satisfaction in functioning eyes and improve functional outcomes in individuals

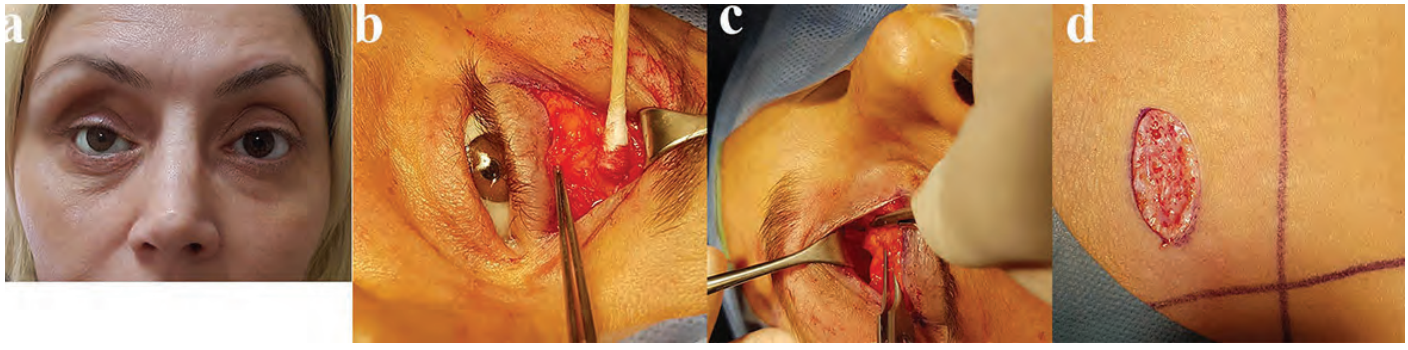

Figure 1. (a) Deep sulcus deformity in the right upper eyelid preoperatively. (b) Opening of the orbital septum after upper eyelid crease incision. (c) View of the atrophic area in the superior-nasal and superior-temporal orbital regions. (d) Dermis fat graft incision from the superior-lateral quadrant of the gluteal region

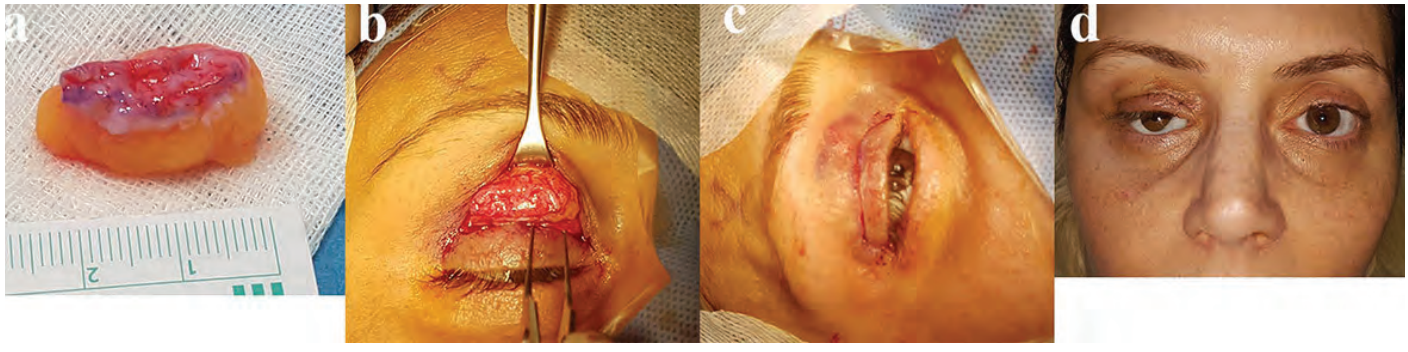

Figure 2. (a) View of the 2×1×0.5 cm dermis fat graft. (b) Dermis fat graft was placed in the atrophic area, with the dermis part facing anteriorly and the fat part posteriorly. (c) View of the last step of surgery after dermis fat graft implantation in which the superior sulcus deformity improves significantly. (d) Follow-up examination on postoperative day 10 showed significant improvement of the upper eyelid sulcus deformity

with ocular prosthesis. Unlike non-autologous materials, one of its greatest advantages is that dermis fat grafts possess no risk of rejection. However, these grafts have a disadvantage of up to 50% risk of graft resorption in the long-term. Furthermore, postoperative complications, including transient supraorbital neuropraxia, liquefied fat discharge from the skin incision, infection, and abscess formation, have been reported in literature (5).

Volume loss in the anophthalmic socket can be intraconal and/or extraconal. Specifically, intraconal volume loss usually leads to enophthalmos, whereas extraconal volume loss often leads to eyelid position problems (1-5). As presented in our case, dermis fat grafts can be utilized for treating deep superior sulcus deformities (5-7). Anchoring the dermis fat graft into the periosteum of the orbital rim can both expand volume and decrease scar tissue formation (5-7). Moreover, dermis fat grafting can cause early ptosis, which typically resolves over time with decreasing tissue edema and fat resorption, as presented in this case (5).

CONCLUSION

In conclusion, dermis fat grafting is an alternative and safe method that can be used to repair intraconal or extraconal volume loss occurring in patients with an anophthalmic socket.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Peer-review: Externally and internally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

REFERENCES

1. Aryasit O, Preechawai P. Indications and results in anophthalmic socket reconstruction using dermis-fat graft. Clin Ophthalmol 2015;9:795-9.
2. Çoban Karataş M, Altan Yaycıoğlu R, Canan H. Orbital Dermis Yağ Greft İmplantasyonu: Primer ve Sekonder İmplant Sonuçları. Turk J Ophthalmol 2015;45:65-70.
3. Sendul SY, Dirim B, Atılgan CU, Demir M, Demir ST, Olgun A, et al. Prosthesis-socket volume imbalance and dermofat graft rehabilitation in patients with an anophthalmic socket. Arq Bras Oftalmol 2020;83:33-8.
4. Modugno AC, Resti AG, Mazzone G, Moretti C, Terreni MR, Albanese G, et al. Long-term outcomes after cosmetic customized prostheses and dermis fat graft in congenital anophthalmia: a retrospective multicentre study. Eye (Lond) 2018;32:1803-10.
5. Rose GE, Collin R. Dermofat grafts to the extraconal orbital space. Br J Ophthalmol 1992;76:408-11.
6. Proffer PL, Czyz CN, Cahill KV, Kavanagh MC, Everman KR, Burns JA, et al. Addition of dermis-fat graft to diminish cable visibility in frontalis suspension for patients with pre-existing deep superior sulci. Ophthalmic Plast Reconstr Surg 2009;25:94-8.
7. Czyz CN, Foster JA, Wulc AE. Superior Sulcus Volumetric Rejuvenation Utilizing Dermis Fat Grafting. Aesthet Surg J 2015;35:892-8.
8. Palamar Onay M, Ceylan N, Yağcı A. Anoftalmik Sokette Gelişen Konjonktiva Kisti Tedavisinde Trikloroasetik Asit Enjeksiyonu. Turk J Ophthalmol 2011;41:389-91.
9. Taner P, Yazici B, Akarsu C, Demirbas E, Ergin A. Anoftalmik Sokette Bakteri Kolonizasyonu. Turk J Ophthalmol 2003;33:484-7.

CASE REPORT

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Imaging Findings of an Aggressive Multicompartmental Venous Vascular Malformation of the Skull Base

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Abstract

Primary vascular lesions are classified as vascular neoplasms and vascular malformations (VMs). Venous VM is the most frequent type of VMs with a prevalence of approximately 1% and is the most common venous anomaly in the head and neck region after hemangioma, but is rarely encountered in the skull base. An expansile growth pattern is noted with permeation into the tissue spaces by adjacent structure invasion, thus presenting with multicompartmental occupation, as in our case. Presented herein is a case of a 12-year-old female patient complaining of left orbital swelling with an aggressive venous VM of the skull base predominantly occupying the left infratemporal fossa extending into various other compartments.

Keywords: Venous vascular malformation, cavernous hemangioma, bright T2W signal, infratemporal fossa, skull base imaging

INTRODUCTION

Primary vascular anomalies were simply categorized into hemangiomas and vascular malformations (VMs) by Mulliken and Glowacki (1) in 1982. Adopting this system based on the histological endothelial characteristics, the International Society for the Study of Vascular Anomalies classified the primary vascular lesions as vascular neoplasms and VMs in 1996 (2). VMs are subclassified into high (fast) flow VMs with arterial components (arterial malformation, arteriovenous malformation, and arteriovenous fistula), low (slow) flow VMs (lymphatic, venous, and capillary), and combined VMs (3). The main difference between vascular neoplasms is their non-proliferative nature despite growing in size with age, as well as non-involution with time in contrast to some vascular neoplasms, such as infantile hemangiomas (4). The previously named cavernous hemangiomas occur anywhere including the cerebral, hepatic, or vertebral cavernous hemangiomas instead of low flow venous VMs. A predilection for the oral cavity, airway, and muscle groups is found in the head and neck region (5). Infratemporal fossa (ITF) is an extremely rare location reported in a few cases in the literature (6).

Accurate preoperative diagnosis is very important to avoid operative complications. Reported are the imaging findings of an aggressive venous VM occupying several skull base compartments but primarily involving the left ITF in a 12-year-old female patient.

CASE PRESENTATION

A 12-year-old female patient presented with left orbital swelling. The head computed tomography (CT) revealed a left ITF mass (Figure 1). The magnetic resonance imaging (MRI) with gadolinium revealed an ITF mass with intermediate signal intensity on T1-weighted (T1W) and bright signal intensity on T2W images, which was not attenuated on fluid-attenuated inversion recovery. The

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lesion extended into the pterygopalatine fossa, sphenoid sinus, posterior nasal cavity, and left cavernous sinus, where it partially surrounded the cavernous internal carotid artery, compressing the left maxillary sinus without invasion. However, by the left lateral orbital wall infiltration, it extended into the extraconal space, displacing the myofascial cone to the right in addition to the left pterygoid process and clival part of the sphenoid bone infiltration (Figure 2). Linear branching signal void areas were observed on the MRI, mimicking flow voids at first appearance. However, most of them were not enhanced on postcontrast images despite the prominent enhancement in the remaining part of the lesion (Figure 2). When simultaneously observed with the previous CT, they correlated with the network of branching calcifications, which are evaluated as widespread phleboliths (Figure 1). No extension was found through the middle cranial fossa but some vasogenic edema in the adjacent temporal lobe without any pathological enhancement, probably due to lesion compression (Figure 2). Venous VM was considered and flow dynamics were evaluated by external carotid artery digital subtraction angiography. Areas of blush-style enhancement from the ophthalmic and maxillary arteries, which were evident in the late venous phases and undetected in the early arterial phase, consistent with low flow VMs, were demonstrated (Figure 3). Surgical treatment was planned following endovascular sclerotherapy with orbital decompression as the first operation. The histopathological examination concluded the venous VM diagnosis (Figure 4).

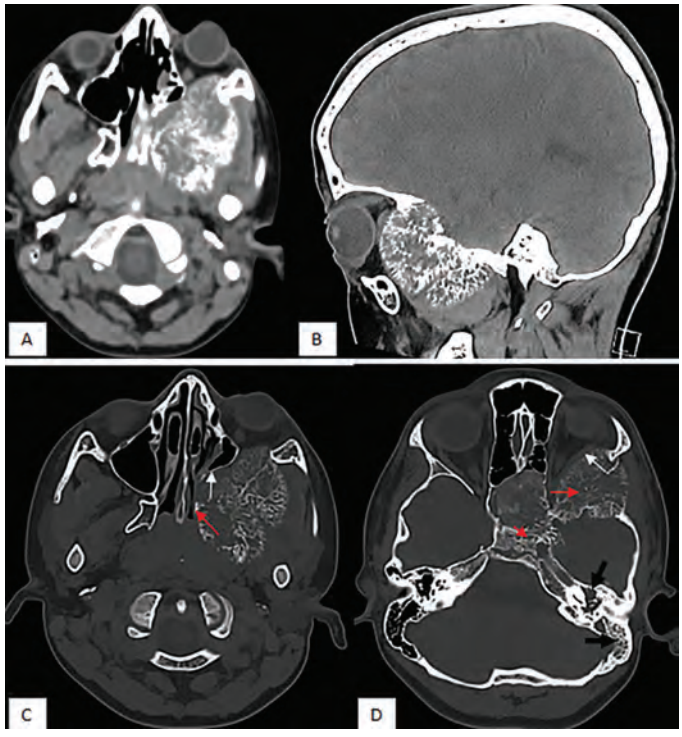

Figure 1. Head CT scan. Axial (A), sagittal (B) images at the intermediate window, and axial (C, D) images at the bone window show the large skull base lesion primarily located in the infratemporal fossa. The network of branching reticular calcifications (phleboliths) is visible throughout the lesion. Note the compression of the left maxillary sinus by the lesion (C; white arrow) and extraconal extension of the lesion with the myofascial cone displacement to the right (D, white arrow). Infiltration of the left lateral orbital wall (D, red arrow), the left pterygoid process (C, red arrow), and clival part of the sphenoid bone (D, short red arrow) are shown. Opacification of the tympanic cavity and mastoid air cells are also marked (D, black arrows)
CT: Computed tomography

DISCUSSION

Venous VM is the most frequent type of VMs with a prevalence of approximately 1% (7) and is the most common venous anomaly in the head and neck region after hemangiomas, but is rarely encountered in the skull base (2). Clinical presentation varies with the involved site. The ITF is a complex space, thus lesions are not realized for a long time until the compressive signs and symptoms associated with the adjacent structures occur, as in our case. In most cases, venous VMs are sporadic, but familial inheritance presented an association with blue rubber bleb nevus, Proteus ve Mafucci syndromes (8). Histologically, VMs are characterized with malformed, ectatic venous channels (phlebiectasis) with a slow stagnant flow that predisposes thrombosis and eventually phleboliths formation, which is the characteristic imaging feature of venous VMs (9). An expansile growth pattern with permeation into the tissue spaces by invading the adjacent structures is observed. The mural muscular anomalies cause the expansile growth pattern (10,11). The radiological examination revealed a frequent finding of phleboliths, which are demonstrated on CT images as calcified linear hyperdensities. However, venous VM in the ITF, which was diagnosed by CT-guided biopsy in a 77-year-old female patient, was reported without this characteristic imaging feature (6), which was due to the early diagnosis with the patient complaining of maxillary sinusitis when the lesion was still small in size. MRI accurately shows the lesion extensions with their superior soft-tissue resolution. Owing to the low cellularity, venous VMs show characteristic bright T2W signals. Prominent contrast enhancement particularly at the late phases (90 s) is also a characteristic. The phleboliths are hypointense on MRI, which are confused with flow voids. However, flow voids are expected to be enhanced with contrast administration, whereas phleboliths are not. In addition, phleboliths show blooming artifacts on gradient-echo sequences. In our patient, the differential diagnosis includes proliferating hemangiomas, which are also hyperintense to the muscle on T2W images but not as bright as venous VMs (12). Juvenile nasopharyngeal

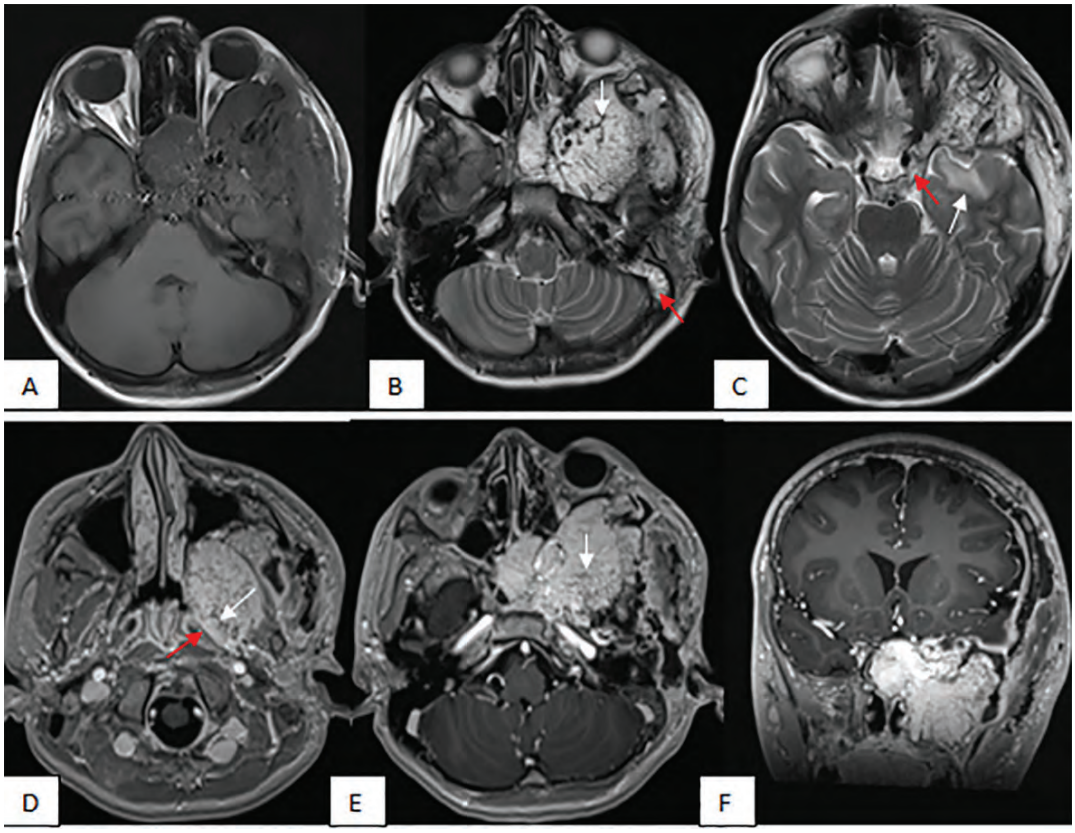

Figure 2: The brain MRI revealed a giant lesion located in its greatest part at the left infratemporal fossa having intermediate signal intensity on axial T1W (A) and bright signal intensity on axial T2W images (B, C) with extensions into the pterygopalatine fossa, sphenoid sinus, and posterior nasal cavity. Note the presence of signal void areas, some of which are in linear branching patterns (B; white arrow). Postcontrast axial (D, E) and coronal (F) images show prominent enhancement of the lesion except for most of the signal void areas (phleboliths) (D, E; white arrows). Note the extension into the left cavernous sinus where the cavernous ICA is partially surrounded (C; red arrow). The retropharyngeal space compression where the cartilaginous portion of the eustachian tube is affected (D; red arrow) resulting in secretory otomastoiditis (B, red arrow) is shown. Note also the edema in the adjacent temporal lobe (C, white arrow). The prominent trans-spatial occupation of the lesion is well demonstrated on the coronal contrast-enhanced T1W image (F)

MRI: Magnetic resonance imaging, T1W: T1-weighted, ICA: Internal carotid artery

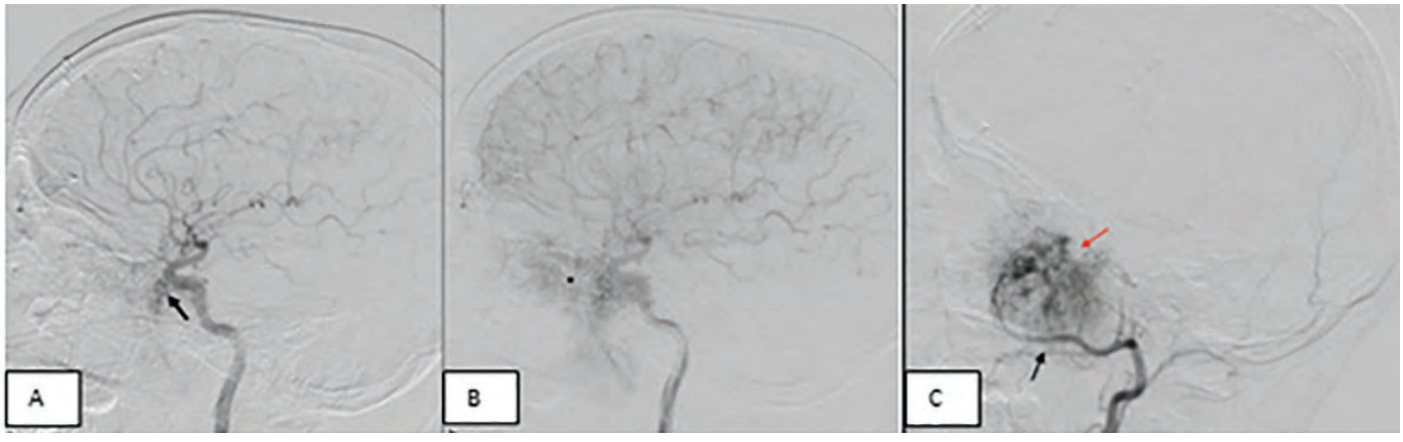

Figure 3: (A, B) DSA of the left ICA in lateral view: A) early arterial and B) late arterial images show the lesion supplied by ophthalmic artery of the ICA (A; arrow) and blush-like enhancement in the late arterial phase (B; asterisk). (C) DSA of the left ECA in lateral view shows the significant feeding of the lesion from the maxillary artery (black arrow) and blush-like enhancement (red arrow). Note the absence of tortuosity in the arterial and venous structures

DSA: Digital subtraction angiography, ICA: Internal carotid artery, ECA: External carotid artery

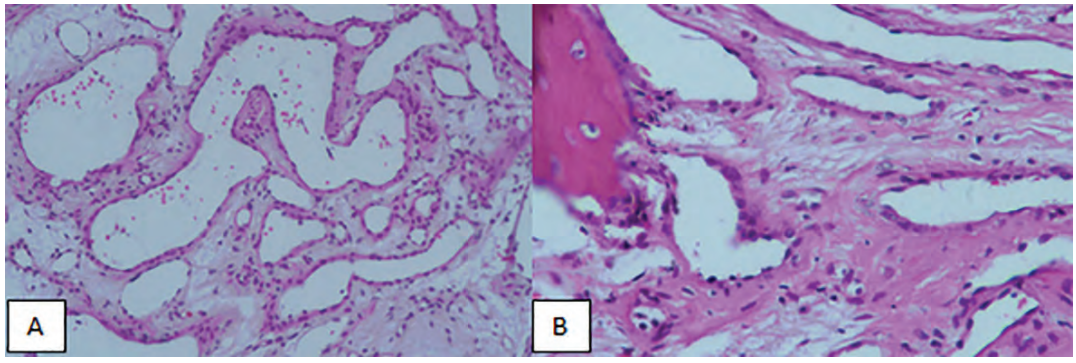

Figure 4: (A) Lesion consisting of thin-walled vascular structures (x200, H&E). (B) Thin-walled vascular structures between bony trabeculae (x400, H&E)
H&E: Hematoxylin and eosin

angiofibromas are other benign, locally aggressive hypervascular tumors of this region but are not associated with phleboliths and the predominant localization in the region of the sphenopalatine foramen and nasal cavity rather than the ITF. The permeative and destructive behavior of the lesion reminds a craniofacial sarcoma at first; however, the bright T2W signal is incompatible with a highly cellular sarcoma.

CONCLUSION

Venous VM should be considered in the differential diagnosis of skull base lesions, and phleboliths with bright T2W signals should be taken into account as distinguishing features.

Ethics

Informed Consent: Written informed consent has been taken from the patient's patents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.E., T.K., E.K., S.A., C.Ç., H.Ö., Design: B.E., T.K., E.K., N.K., Data Collection or Processing: O.İ., B.E., Analysis or Interpretation: B.E., S.A., C.Ç., H.Ö., Literature Search: Ö.İ., B.E., N.K., Writing: B.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 1982;69:412-22.
2. Lowe LH, Marchant TC, Rivard DC, Scherbel AJ. Vascular malformations: classification and terminology the radiologist needs to know. Semin Roentgenol 2012;47:106-17.
3. Resnick D. Vascular and lymphatic tumors. In: Draud LA, Fix CF, editors. Diagnosis of bone and joint disorders. 4th ed. Philadelphia, Pa: Saunders, 2002.4186-95.
4. Connor SE, Flis C, Langdon JD. Vascular masses of the head and neck. Clin Radiol 2005;60:856-68.
5. Buckmiller LM, Richter GT, Suen JY. Diagnosis and management of hemangiomas and vascular malformations of the head and neck. Oral Dis 2010;16:405-18.
6. Nagaoka M, Morino T. Venous malformation in the infratemporal fossa diagnosed by CT-guided core needle biopsy. BMJ Case Reports 2021;14:e238171.
7. Legiehn GM, Heran MK. Venous malformations: classification, development, diagnosis, and interventional radiologic management. Radiol Clin North Am 2008;46:545-97, vi.
8. Dubois J, Alison M. Vascular anomalies: what a radiologist needs to know. Pediatr Radiol 2010;40:895-905.
9. Hochman M, Adams DM, Reeves TD. Current knowledge and management of vascular anomalies, II: malformations. Arch Facial Plast Surg 2011;13:425-33.
10. Flors L, Leiva-Salinas C, Maged IM, Norton PT, Matsumoto AH, Angle JF, et al. MR imaging of soft-tissue vascular malformations: diagnosis, classification, and therapy follow-up. Radiographics 2011;31:1321-40; discussion 1340-1.
11. Dubois J, Soulez G, Oliva VL, Berthiaume MJ, Lapierre C, Therasse E. Soft-tissue venous malfor- mations in adult patients: imaging and therapeutic issues. Radio Graphics 2001;21:1519-31.
12. Navarro OM, Laffan EE, Ngan BY. Pediatric soft-tissue tumors and pseudo-tumors: MR imaging features with pathologic correlation: part 1. Imaging approach, pseudotumors, vascular lesions, and adipocytic tumors. Radiographics 2009;29:887-906.

CASE REPORT

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Eur Arch Med Res 2021;37(3):199-202

Eccrine Porocarcinoma: A Case Report

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Abstract

Eccrine porocarcinoma is a rare carcinoma but it is the most common malignant sweat gland tumor. It can develop *de novo* or from poroma ground. It is mostly seen in elderly patients and the most common locations are the lower limbs, the trunk, and the head and neck. This condition is an important differential diagnosis in several clinical entities. We present a case of eccrine porocarcinoma diagnosed clinically and histomorphologically. We also reviewed the available information on this condition from published literature.

Keywords: Eccrine porocarcinoma, head and neck tumors, cutaneous adnexal tumors

INTRODUCTION

Eccrine porocarcinoma, initially defined as epidermotropic eccrine carcinoma in 1963 by Pinkus and Mehragen (1), is a rare malignant sweat gland tumor originating from acrosyringeal cells. It is the most common malignant sweat gland tumor and constitutes 0.005-0.01% of all cutaneous tumors (2). It can develop *de novo* from normal sweat gland cells, as well as from malignant transformation of poroma ground. It is more common in women and in elderly patients. Clinically, eccrine porocarcinoma presents as a papule, plaque, nodule, or polyp which may have ulcerations. The most common locations are the lower extremities, the trunk, and the head and neck, but it can develop in any location (3). It is characterized histopathologically by large anastomosed epithelial islands associated with the epidermis and may extend deep. Intercellular bridges can be seen between cells while peripheral palization is not observed (4). Wide local excision is the best treatment option (5).

In this case report, we present a case of eccrine porocarcinoma developing on the malar region on both sides of an 82-year-old female patient who was previously diagnosed with high-grade carcinoma.

CASE PRESENTATION

An 82-year-old female patient had lesions on the bilateral malar regions that started 1 year ago. On physical examination, there was a 4 cm, elevated tumoral lesion, with irregular borders, hyperemic periphery, and hemorrhagic surface on each malar region. Punch biopsy was performed due to suspicion of malignancy (Figure 1). Both lesions were excised after the biopsy result reported high-grade squamous cell carcinoma.

On macroscopic examination, the tumor from the right malar region was seen 1.5 cm raised from the skin, measured 3.5x2.5 cm, and had irregular borders. The tumor from the left malar region was raised 1.7 cm from the skin, measured 4x2.5 cm, and also had irregular borders.

Microscopic examination revealed a tumoral formation consisting of trabeculae of different sizes that were anastomosed to each other and were continuous with the epidermis (Figure 2). Although the tumor mostly showed an expansive growth pattern, invasive areas were also seen. Tumor cells consisted of basaloid cells with prominent cytological atypia, hyperchromatic nucleus, nucleolar prominence, high mitotic activity, and prominent pleomorphism (Figure 3). Cells with

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clear cytoplasm and focal squamous cell differentiation were seen in some areas (Figure 4). Areas of ductal differentiation and rare intracytoplasmic lumen formation were detected (Figure 5). Necrosis was seen in the middle of the tumor islands. Upon histochemical study, periodic acid-Schiff (PAS) positivity was observed in clear cell areas. In neoplastic cells, the following immunohistochemical findings were observed: Diffuse positive staining with CK5-6, p63, and EMA, focal positive staining with CD117, positive staining with carcinoembryonic antigen (CEA) in ductal differentiation areas, and negative staining with BerEp4 (Figure 6). The Ki-67 proliferative index was 65-70% (Figure 7). These histomorphological and immunohistochemical findings confirm the diagnosis of eccrine porocarcinoma for both lesions.

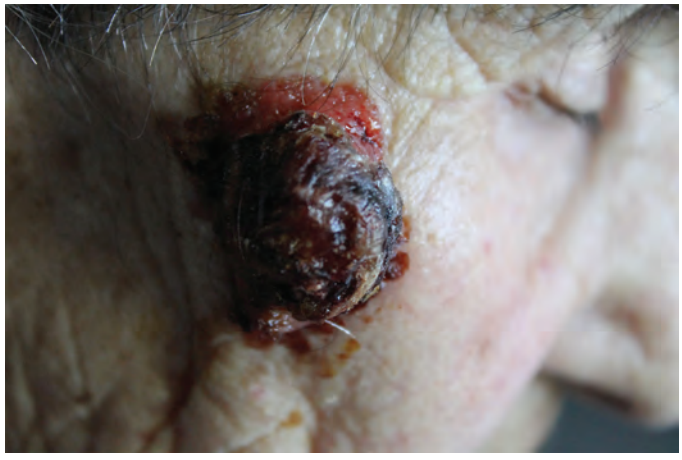

Figure 1. Tumoral lesions located in both malar regions, with irregular surface and borders, and hemorrhagic surface

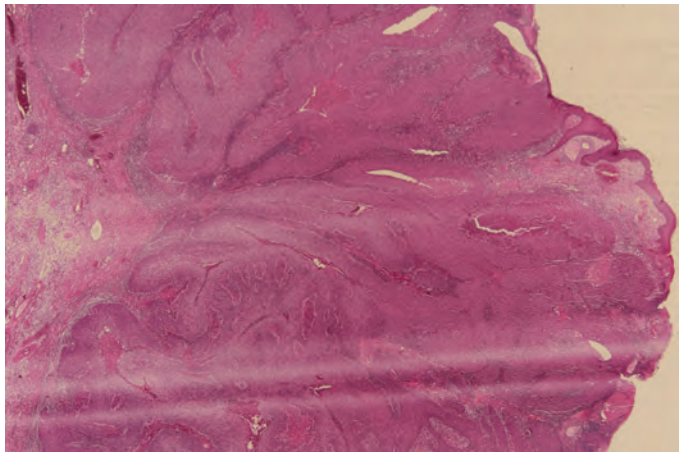

Figure 2. Tumor islands anastomosing with each other showing continuity with the epidermis (H&Ex20)
H&E: Hematoxylin and eosin

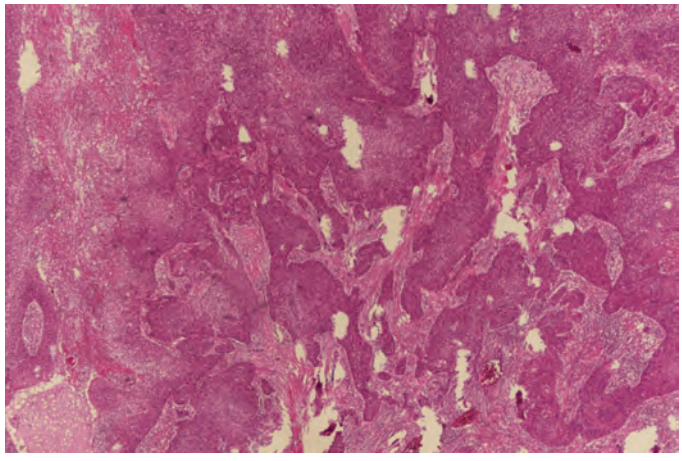

Figure 3. Tumor cells showing large tumor islands and an infiltrative growth pattern. (H&Ex40)
H&E: Hematoxylin and eosin

DISCUSSION

Eccrine porocarcinoma is a rare malignant sweat gland tumor that can develop *de novo* or from poroma ground. Clinically, it can be confused with seborrheic keratosis, pyogenic granuloma, verruca, or squamous cell carcinoma (6). Eccrine

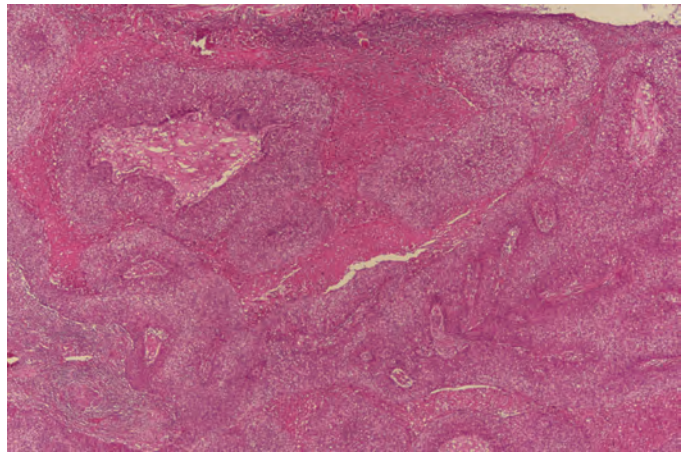

Figure 4. Note clear cell change and necrosis (H&Ex40)
H&E: Hematoxylin and eosin

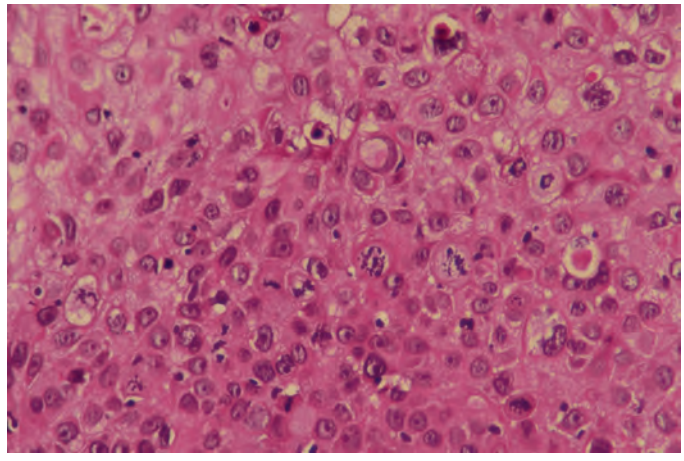

Figure 5. Tumor cells showing cytological atypia, mitosis, and pleomorphism. Note the intracytoplasmic lumen (H&Ex400)
H&E: Hematoxylin and eosin

porocarcinoma has a high risk of recurrence and metastasis. Mortality rate is highly correlated with the presence of metastases (7). The more common invasive form shows an infiltrative or expansive growth pattern in addition to *in situ* areas. Tumor cells continuing with the epidermis consist of trabeculae that anastomose with each other in an asymmetrical appearance. Cytologically, high mitotic activity, pleomorphism, nuclear atypia, and nucleolar prominence are seen. Necrosis is common. Ductal differentiation areas, intracytoplasmic lumen, focal squamous differentiation areas, and clear cell change can be seen (7-10). Rarely, sebaceous differentiation areas may accompany (11).

Immunhistochemical findings can show overexpression with P53 and negative staining with S100 and BerEP4 but these do not have a significant role in the diagnosis. Demonstrating ductal differentiation areas immunohistochemically with CEA and epithelial membrane antigen (EMA) is more helpful in diagnosis and can also be demonstrated histochemically with D-PAS (12,13).

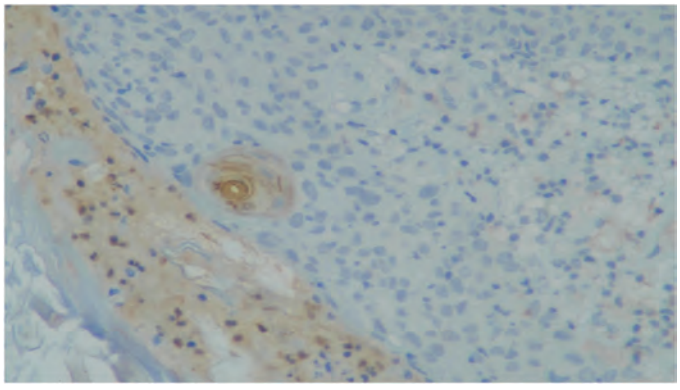

Figure 6. Positive staining with CEA in cells showing ductal differentiation by immunohistochemistry
CEA: Carcinoembryonic antigen

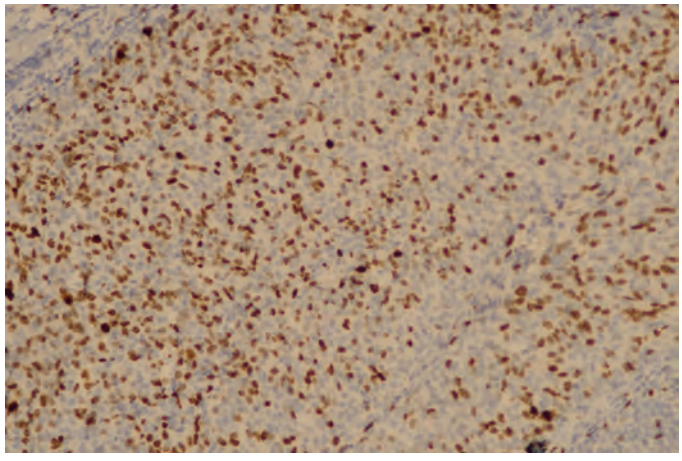

Figure 7. Ki-67 proliferation index

In a study by Robson et al. (14), the relationship between tumor size, prognosis, or lymph node involvement could not be demonstrated. However, involvement deeper than 7 mm and lymph node involvement were found to be associated with poor prognosis. High mitotic index and lymphovascular invasion have also been shown to be associated with poor prognosis (14). Our case shows high mitotic activity and the depth of the tumor is more than 7 mm. There were no lymph node metastasis and distant organ metastasis during follow-up.

Benign skin appendix tumors, squamous cell carcinoma, basal cell carcinoma, malignant melanoma, and metastatic carcinomas should also be included in the differential diagnosis in cases of eccrine porocarcinoma. It can be distinguished from benign skin appendix tumors by the presence of invasive areas, cytological atypia, and pleomorphism. Differential diagnosis with squamous cell carcinoma can be made by the presence of ductal differentiation areas and *in situ* areas. Absence of peripheral palization and immunohistochemically BerEp4 negativity may be helpful in the differential diagnosis from basal cell carcinoma. The presence of negative staining with s100 immunohistochemically and positive staining with cytokeratin are helpful in the differential diagnosis of malignant melanoma.

CONCLUSION

Eccrine porocarcinoma is a rare malignant sweat gland tumor with a high risk of recurrence and metastasis. It is included in the differential diagnosis of several clinical entities, including benign skin appendix tumors, basal cell carcinoma, squamous cell carcinoma, and metastatic carcinomas. Despite being rare, eccrine porocarcinoma is the most common sweat gland tumor and should always be considered in able to determine the prognosis and the correct treatment of this disease.

Ethics

Informed Consent: Verbal consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.B.G., Ö.Y., E.M., Concept: A.B.G., Ö.Y., Design: A.B.G., Ö.Y., E.M., Data Collection or Processing: A.B.G., Ö.Y., E.M., Analysis or Interpretation: A.B.G., Ö.Y., Literature Search: A.B.G., Ö.Y., Writing: A.B.G., Ö.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Pinkus H, Mehregan AH. Epidermotropic eccrine carcinoma. A case combining features of eccrine poroma and Paget's dermatosis. Arch Dermatol 1963;88:597-606.
2. Nazemi A, Higgins S, Swift R, In G, Miller K, Wysong A. Eccrine Porocarcinoma: New Insights and a Systematic Review of the Literature. Dermatol Surg 2018;44:1247-61.
3. McGuire C, Fadel Z, Samargandi O, Williams J. Primary eccrine porocarcinoma of the thumb with multiple metastases: a case report and review of the literature. Case Reports Plast Surg Hand Surg 2019;6:88-91.
4. Torbeck R, Fazio J, Lee JB, Trufant J. Eccrine porocarcinoma presenting as a recurrent wart. Cutis 2019;103:166-8.
5. Ekmekci S, Lebe B. Eccrine Porocarcinoma of the Scalp. Turk Patoloji Derg 2013;156-9.
6. Devi NR, Valarmathi K, Lilly M, Satish S, Mishra N. Primary Axillary Porocarcinoma: A Rare Cutaneous Tumour. J Clin Diagn Res 2016;10:ED04-6.
7. Cardoso JC, Calonje E. Malignant sweat gland tumours: an update. Histopathology 2015;67:589-606.
8. Shen J, Pan X, Lu Y, Pan D, Ma Y, Zhan R. A case of eccrine porocarcinoma characterized by a progressive increase in the level of Ki-67 index: case report and review of literature. BMC Surg 2019;19:142.
9. Kitamura K, Kinehara M, Tamura N, Nakamura K. Hidroacanthoma simplex with invasive growth. Cutis 1983;32:83-4, 86-8.
10. Bardach H. Hidroacanthoma simplex with in situ porocarcinoma. A case suggesting malignant transformation. J Cutan Pathol 1978;5:236-48.
11. Kazakov DV, Kutzner H, Spagnolo DV, Kempf W, Zelger B, Mukensnabl P, et al. Sebaceous differentiation in poroid neoplasms: report of 11 cases, including a case of metaplastic carcinoma associated with apocrine poroma (sarcomatoid apocrine porocarcinoma). Am J Dermatopathol 2008;30:21-6.
12. Wollina U, Castelli E, Rülke D. Immunohistochemistry of eccrine poroma and porocarcinoma--more than acrosyringeal tumors? Recent Results Cancer Res 1995;139:303-16.
13. Gu LH, Ichiki Y, Kitajima Y. Aberrant expression of p16 and RB protein in eccrine porocarcinoma. J Cutan Pathol 2002;29:473-9.
14. Robson A, Greene J, Ansari N, Kim B, Seed PT, McKee PH, et al. Eccrine porocarcinoma (malignant eccrine poroma): a clinicopathologic study of 69 cases. Am J Surg Pathol 2001;25:710-20.

LETTER to the EDITOR

DOI: 10.4274/eamr.galenos.2021.82621
Eur Arch Med Res 2021;37(3):203

Radiological Figure Quality and Compatibility in Published Articles

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University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital, Clinic of Radiology Service, İstanbul Turkey

Keywords: Radiological image, figure, figure legend

Dear Editor,

We read with great interest, the case report by Tutar et al. (1) entitled "Lymphoepithelioma of Larynx: Case Report", which was published in December 2020 (volume 36, issue 4) in the *European Archives of Medical Research*. The authors presented a rare case in this didactic, well-designed, and well-illustrated article. However, necessary matters are pointed out about the radiological figure. The authors mentioned, "The lesion invaded the arytenoid cartilage and extended into the paralaryngeal area and fat planes (Figure 2a, b)". However, Figure 2 presented two axial contrast-enhanced neck computed tomography images with almost the same level and location in the soft tissue window. The multiplanar reconstructed images were not chosen, particularly the coronal planes, to show the lesion extensions through the laryngeal area and the destruction of the mentioned cartilaginous structures. Therefore, the presence of lesion invasion in the arytenoid cartilage is unclear. These figures do not meet the terms mentioned in the article. Furthermore, figure legends or notations were not provided. The authors and persons responsible for the peer-review processes are reminded to pay particular attention to this issue in such well-designed articles, where didactic quality is at the forefront.

The main problem of an article without a radiologist co-author was reported as follows: Unacceptable poor quality figure legends, unmentioned imaging modality, undescribed imaging findings, unblinded patient data, and low image quality (poor spatial orientation, poor image resolution, suboptimal contrast, and absent or poor cropping). A study by Luyckx et al. (2) concluded that involving a radiologist as co-author in the publication significantly improves its quality.

Ethics

Peer-review: Internally peer-reviewed.

Concept: S.A., Design: S.A., E.K., Data Collection or Processing: S.A., T.K., Analysis or Interpretation: S.A., H.Ö., Literature Search: S.A., E.K., T.K., H.Ö., Writing: S.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Tutar B, Akgün F, Ahmed İA, Berkiten G, Saltürk Z, Uyar Y, Özay Nayır P. Lymphoepithelioma of Larynx: Case Report. Eur Arch Med Res 2020;36:285-8.
2. Luyckx E, Bosmans JML, Broeckx BJG, Ceyssens S, Parizel PM, Snoeckx A. Radiologists as Co-Authors in Case Reports Containing Radiological Images: Does Their Presence Influence Quality? J Am Coll Radiol 2019 Apr;16(4 Pt A):526-7.

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