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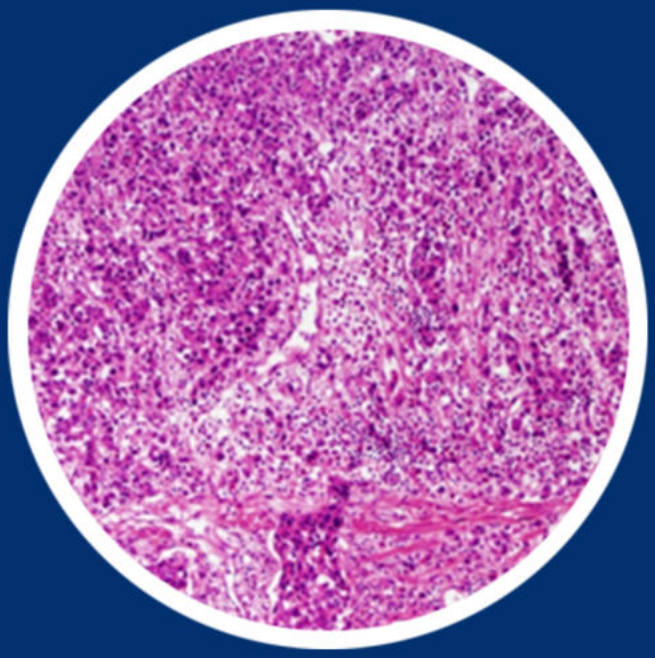

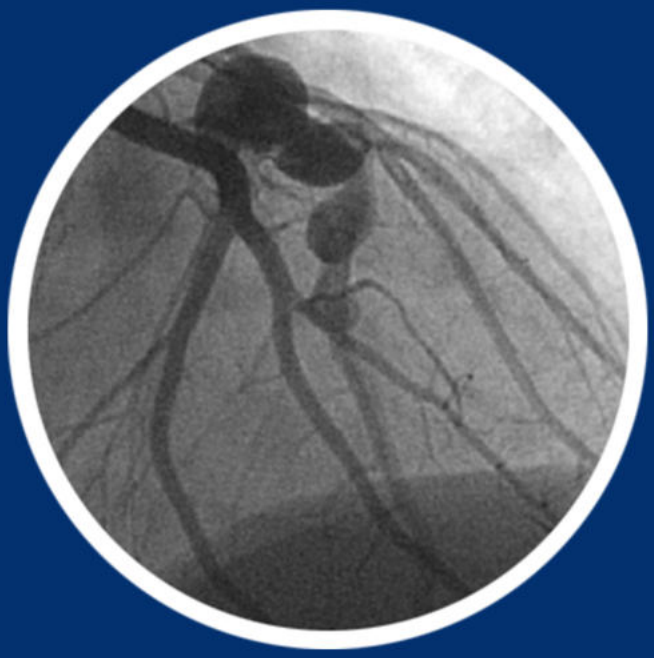

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The European Research Journal 2020;6(4):270-275 Original Article

DOI: 10.18621/eurj.645852 *Infectious Diseases and Clinical Microbiology*

Tenofovir plus entecavir combination therapy for chronic hepatitis B with nucleos(t)ide analogue failure

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ABSTRACT

Objectives: Currently, both entecavir (ETV) and tenofovir (TDF) are recommended first-line therapy for chronic hepatitis B treatment due to good tolerance, lower side-effect profile and high genetic barrier. However, mutations that may develop in the polymerase gene during treatment may result treatment failure. In this study, we aimed to evaluate the efficacy and virologic response of ETV plus TDF combination therapy in chronic hepatitis B patients with suboptimal response to nucleos(t)ide analogues (NAs) monotherapy.

Methods: A total of 813 patients who were followed-up with the diagnosis of chronic hepatitis B and who were treated with TDF or ETV monotherapy were screened. Patients who had a partial or non response to monotherapy during at least 12 months and who was the presence of serum HBV-DNA levels ≥ 2000 IU/mL at the time of initiation of the ETV plus TDF combination therapy were included.

Results: Ten (1.2%) patients (9 TDF, 1 ETV) were identified to have had partial response (50%) or breaktrough (40%) or virologic rebound (10%) to monotherapy. The median age was 36.8 years (range, 22-55 years), and 5/10 (50%) patients were male. Of 10 patients, nine of achieved undetectable HBV-DNA (< 15 IU/mL) levels (50% of in 6 months and 90% of in 18 months) with combination therapy. One patient showed no response.

Conclusions: Our results suggest that combination therapy is superior to the antiviral change in treatment failure with NAs. In addition, it is important to conduct HBV drug resistance analyzes to prevent false drug change in treatment.

Keywords: Combination therapy, chronic hepatitis B, virologic response, entecavir, tenofovir

The main outcome of the chronic hepatitis B therapy is to achieve hepatitis B surface antigen (HBsAg) seronconversion, however this rate is about 1-2%. The second goal of treatment is to prevent progression to cirrhosis and hepatocellular carcinoma, improve quality of life and survival by providing complete virologic response [1]. It is known that high HBV-DNA level is risk factor for disease progression in patients with chronic hepatitis B [1, 2]. Thus, successful management of patients is important for suppressing continuous virologic replication (CVR) and for the remission of liver disease. Nucleos(t)ide analogs (NAs) are the main anti-HBV agents that inhibit HBV replication by targeting the reverse transcriptase region of the hepatitis B virus (HBV) polymerase [3]. However, a long term of treatment may increase the development of drug resistance that can lead to rebound in HBV replication and exacerbation of HBV-related disease [3].

Currently, six NAs are licensed in our country;

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lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LdT), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF). Lamivudine (LAM) was the first oral antiviral agent for chronic hepatitis B. However, the use of LAM is limited because it is associated with a high rate of antiviral resistance and increases up to 65-70% after 5 years of treatment [4]. For patients with LAM resistant, ADV has been used as a rescue therapy but, its antiviral effect is not optimal [5]. Among them, both entecavir and tenofovir are recommended first-line therapy for chronic hepatitis B due to good tolerance, lower side-effect profile and high genetic barrier [6, 7]. The prevalence of ETV resistance in the five-year follow-up is only 1.2%. However, it increases to 50% in patients with lamivudine resistance [8]. TDF resistance was not detected in patients with chronic hepatitis B for 8 years compared with ETV [9].

In this study, we aimed to evaluate the efficacy and virologic response of ETV plus TDF combination therapy in chronic hepatitis B patients with suboptimal response to NAs monotherapy.

METHODS

Patient Selection

Between November 2007 - September 2019, a total of 813 patients who were followed-up with the diagnosis of chronic hepatitis B and who were treated with TDF or ETV were screened. The patients who had a partial or non response to TDF or ETV monotherapy during at least 12 months and who was the presence of serum HBV-DNA levels ≥ 2000 IU/mL at the time of initiation of the combination therapy were included in the study. Patients with nonalcoholic fatty liver disease, autoimmune hepatitis, chronic hepatitis C, hepatitis D virus superinfection, or HIV co-infection were excluded. Patients were received TDF 245 mg and ETV 0.5 mg/1 mg once daily.

Laboratory Assessments

HBsAg, HBeAg, anti HBe, anti HBcIgG, Anti HBs, Anti HCV and Anti HDV were studied with ELISA (Liaison, Diasorin, Italy). HBV-DNA levels were studied with real-time polymerase chain reaction (PCR). (COBAS Ampli Prep/COBAS, TaqMan; lower limit of quantification, 15 UL/mL). HBV genotypic resistance mutations were assessed by Multiplex PCR-Revers Hibridizasyon (Inno-Lipa HBV DR v2. Innogenetics, Belgium) Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Tbil), direct bilirubin (Dbil) were determined with AU5800 auto-analyzer (Beckman Coulter Inc., CA, USA). Alpha Fetoprotein (AFP) was analyzed with the DxI 800 auto-analyzer (Beckman Coulter Inc., CA, USA). Prothrombin time (PT) was studided by CS-2500 automated coagulation analyzer (Sysmex Corporation, Kobe, Japan). International normalized ratio (INR) was calculated using INR = patient PT/mean normal PT formula. The platelet (PLT) was analyzed by Beckman Coulter LH 780 (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland). ISHAK scoring system was used to determine the liver inflammation and fibrosis stages. The serum HBV-DNA level was assessed every three months during the first 12 months.

Definitions

Virological response is defined as undetectable HBV-DNA with a limit of detection of 15 IU/mL. Primary nonresponse is defined as a decrease in serum HBV-DNA <1 log10 after three months of therapy. Partial virological response is defined as a decrease in HBV-DNA of >2 log10 IU/mL but detectable HBV-DNA after at least 12 months of therapy. Virological breakthrough is defined as an increase in HBV-DNA of >1 log10 IU/mL in comparison with the baseline at any time during treatment.

RESULTS

Of the 813 patients 684 (84.1%) were treatment-naive, 129 (15.9%) were treatment experienced (42 lamivudine, 22 adefovir and 65 peginterferon) before initiating ETV or TDF monotherapy. Among them, 395 were treated with TDF and 418 were treated with ETV, and virologic response rate was 97.7% in the TDF group and 99.7% in the ETV group.

Ten (1.2%) patients (9 TDF, 1 ETV) were identified to have had partial response (50%) or breaktrough (40%) or virologic rebound (10%) to monotherapy and were treated with a combination of ETV and TDF. One patient had liver cirrhosis and 9

Table 1. Baseline characteristics and laboratory values of study patients

Patients	MA	ŞŞ	EP	FG	ŞA	ÖG	EG	KL	CÇ	HA
Age (years)	26	42	30	49	50	22	24	55	48	22
Gender	F	M	F	F	M	M	M	F	F	M
Baseline HBV-DNA (IU/mL)	3.5 $\times10^4$	9.7 $\times10^2$	1.2 $\times10^3$	1.7 $\times10^8$	1.5 $\times10^5$	5.5 $\times10^3$	7.1 $\times10^5$	2.1 $\times10^5$	9.8 $\times10^5$	6.5 $\times10^3$
HBeAg (S/CO)	+	-	+	+	+	+	+	-	+	+
Anti HBe (S/CO)	-	+	-	-	+	-	-	+	-	-
ALT (U/L)	58	255	71	425	39	32	255	68	57	36
AST (U/L)	56	142	44	233	30	27	95	40	38	29
Bilirubin (mg/dL)	0.5	1.1	0.7	0.9	0.7	0.8	1.5	0.9	0.7	1.0
Albumin (g/dL)	4.1	5	4.4	3.3	4	4.5	4.9	4.0	4.1	4.3
PLT (K/uL)	234	239	325	275	142	316	214	141	163	274
INR	0.9	0.9	1.1	0.9	1	1.2	1.1	0.9	0.9	1.1
AFP(IU/mL)	1.6	1,8	5.4	2.9	4.1	2.5	2.9	2.4	5.3	4.8
HAI (Ishak scale)	9	7	4	8	7	5	7	4	8	3
Fibrosis (Ishak scale)	2	3	2	3	5	1	3	2	3	2

F = female, M = male, (+) = positive, (-) = negative, HBV = hepatitis B virus, DNA = deoxyribonucleic acid, AST = Aspartat aminotransferaz, ALT = alanine aminotransferase PLT = platelet, INR = international normalized ratio, AFP = Alpha Fetoprotein, HAI = Histology Activity Index

patients were non-cirrhotic. The patient with cirrhosis received entecavir 1 g/day plus tenofovir 245 mg/day. The mean duration of combination therapy was 46.1 months (range, 14-60 months). Baseline characteristics and laboratory values of patients are summarized in Table 1. The median age was 36.8 years (range, 22-55 years), and 5/10 (50%) patients were male. The median baseline HBV-DNA was 1.72E+6 IU/mL (9.7E+2 - 1.7E+8) and 8/10 patients were HBeAg positive.

HBV resistance mutation to LAM (rt 80, rt 173, rt 180, rt 204 (lipa v2)) was detected in two patients. No

Table 2. HBV-resistance mutation profiles of patients

	Resistance Mutation to LAM rtL80, rtV173, rtL180, rtM204 (lipa v2)	Resistance Mutation to ADV rtA181T/V, rtN236T (lipa v2)
Patient 1 (MA)	No resistance mutation	No resistance mutation
Patient 2 (ŞŞ)	No resistance mutation	No resistance mutation
Patient 3 (EP)	Rt180m, 204v mutation	No resistance mutation
Patient 4 (FG)	No resistance mutation	No resistance mutation
Patient 5 (ŞA)	No resistance mutation	No resistance mutation
Patient 6 (ÖG)	No resistance mutation	No resistance mutation
Patient 7 (EG)	No resistance mutation	No resistance mutation
Patient 8 (KL)	Rt180m, 204v mutation	No resistance mutation
Patient 9 (CÇ)	No resistance mutation	No resistance mutation
Patient 10 (HA)	No resistance mutation	No resistance mutation

LAM = lamivudine, ADV = adefovir dipivoxil

resistance mutation to ADV (rtA181T/V, rt N236T (lipa v2) was detected (Table 2). One of the two patients with lamivudine resistance received 1 g/day ETV and the other one received 0.5 g/day ETV due to side effects. HBeAg seroconversion was observed in 2 of 8 patients after combination therapy at 4 and 22 weeks. There was no difference between HBeAg-positive and HBeAg negative patients in the characteristics of virological response; 9/10 (90%) patients achieved undetectable HBV-DNA (< 15 IU/mL) levels (50% of in 6 months and 40% of in 18 months). Virological response was observed in the 60th month in the patient receiving ETV 0.5 g/day with lamivudine resistance and in the 52th month in the cirrhotic patient. One patient who had no virological response was receiving TDF 245 plus ETV 1 g/day due to lamivudine resistance.

Combination therapy was well tolerated, and no clinically significant side effects and treatment discontinuations were observed. No ALT/AST flares (> 3 upper limit of normal) and increase in creatinine levels were observed during the follow-up period.

DISCUSSION

The limitation of treatment with NAs is the development of HBV resistance variants that can lead to treatment failure and exacerbation of HBV related disease, especially using low potent and low genetic barrier NAs. Mutations in the polymerase gene may cause cross resistance to other NAs and may result virologic breakthrough, biochemical breakthrough. Today, both ETV and TDF were recommended as first-line therapy for chronic hepatitis B drugs due to high potency and higher genetic barrier. Virologic response rate was found 97.7% with TDF and 99.7% with ETV in the patients we followed, partial response (50%) or breaktrough (40%) or virologic rebound (10%) to monotherapy were identified in 10 patients. In a multicenter study evaluating the long-term efficacy of TDF and ETV in NAs naive HBeAg positive patients, no significant difference was found between the two drugs in terms of virologic response and tolerability during 144 weeks follow-up [10]. Similar results were confirmed in other studies [11, 12].

In the present study we analysed the efficacy of TDF plus ETV combination therapy in patients who were failed to TDF or ETV monotherapy due to incomplete response or genotypic resistance. Of patients 90% were achieved undetectable HBV-DNA (< 15 IU/mL) levels and combination therapy was found to have more suppressive effect on virologic suppression. Chung *et al*. [13] compared the the efficacy of maintenance TDF monotherapy with TDF plus ETV combination therapy in 201 multidrug-resistant chronic hepatitis B patients who were previously treated with ETV plus TDF combination therapy and achieved complete virologic suppression. Among them, 153 were treated with ETV plus TDF combination therapy and 48 were treated TDF monotherapy. During follow up virologic breakthrough was developed in five patients; one patient in TDF monotherapy group and four patients in combination therapy group and there were no significant differences between groups. They reported that there was no additional risk of virologic breakthrough with TDF monotherapy after complete virologic suppression [13]. Chen *et al*. [14] compared the efficacy between TDF (212 patients) and TDF plus ETV (196 patients) combination therapy with a poor response to ETV. They reported that combination therapy was not superior to TDF monotherapy after the consideration of the rate of viral supression at weeks 24 and 48 [14]. This finding was supported by a study performed by Kim *et al*. [15]. They were explored the persistence of CVR on 76 antiviral resistant chronic hepatitis B patients showing CVR on TDF plus ETV (n = 52), TDF plus LAM (n = 14), and TDF plus LdT (n = 10) combination therapy, who were switched to TDF monotherapy. The median duration of combination therapy was 20.8 months and the median follow-up period was 24.7 months after switching to TDF monotherapy and all patients maintained CVR and switching from combination therapy to TDF monotherapy has been reported to be good in in virologically suppressed chronic hepatitis B [15]. Li *et al*. [16] compared the efficacy of TDF switch therapy in 50 chronic hepatitis B patients with suboptimal response to ADV-based combination therapy. Among them 17, 14 and 19 patients were previously treated with LAM plus ADV, LdT plus ADV and ETV plus ADV, respectively. A total of 41

patients were treated with TDF and nine with TDF plus ETV and the virologic response at week 48 and 96 was reported 76.0 and 89.8%, respectively. Among them, three patients (two of treated with TDF and one of with TDF plus ETV) had suboptimal response and six patients (five of received TDF and one of received TDF plus ETV) had virologic breakthrough. They reported that TDF switch therapy is efficient and safe for patients with chronic hepatitis B with a suboptimal response to ADV-based combination therapy [16].

HBV resistance mutation to LMV (rt 80, rt 173, rt 180, rt 204 (lipa v2) was detected in two patients. Entecavir dose is recommended 1 mg/day if the patient is lamivudine experienced or or has decompensated cirrhosis [17]. In our patient with lamivudine resistance, the virological response was seen in the patient receiving entecavir 0.5 g/day, but no response occurred in the patient receiving entecavir 1 g/day. Non-response to treatment was not affected by lamivudine resistance, but was considered to be associated with history of renal transplantation and receiving immunosuppressive therapy of this patient.

No resistance mutation to ADV (rtA181T/V, rt N236T (lipa v2) was detected. in the study published by Park *et al*. [18], 63 chronic hepatitis B patients with genotypic resistance to LAM who showed a suboptimal response to LAM and ADV combination therapy were evaluated. Among patients, 30 were treated with ETV plus ADV and 33 were treated with ETV plus TDF for 12 months. They found 84.8% virologic response rate in ETV plus TDF group [18]. This result was supported by a recent study that performed by Li *et al*. [19]. They were analyzed the efficacy of ETV monotherapy versus ETV-TDF combination therapy in 220 LAM resistant chronic hepatitis B patients; 114 patients were treated with ETV monotherapy and 106 were treated with ETV-TDF combination therapy for at least 24 months. They reported that combination group was superior to the ETV group in achieving a virologic response [19]. Combination therapy was well tolerated, and no clinically significant side effects and treatment discontinuations were observed. No ALT/AST flares (> 3 upper limit of normal) and increase in creatinine levels were observed during the follow-up period. On the other hand, given the economic benefit and ease of use, monotherapy can be a better choice after archieve viral suppression.

CONCLUSION

In conclusion, our results showed combination therapy was superior in the failure of treatment with nucleos(t)ide analogues. In addition, HBV drug resistance analyzes are important to prevent wrong drug changes in treatment. However, further large-scale and long-term follow-up prospective studies are needed to explain these results.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Informed consent

Informed consent was obtained from all participants included in the study.

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Factors effecting the outcomes of artificial urinary sphincter placement: a single-center study

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ABSTRACT

Objectives: To evaluate the patients who underwent artificial urinary sphincter (AUS) placement and report outcomes of the procedure.

Methods: From March 2008 to February 2017, the data of patients who have undergone AUS placement were evaluated retrospectively. Age, body-mass index (BMI), comorbidities, education level, previous radiotherapy (RT) history of the patients were recorded. Cognitive status was examined using the Mini Mental Status Examination test (MMSE). International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) was completed pre- and post-operatively. Quality of life and satisfaction of patients were evaluated using Patient Global Impression of Improvement (PGI-I) scale. To analyze factors effecting success and revision rates, patients were grouped according to age, BMI, comorbidities, smoking habbit, previous RT history and etiology of incontinence. Treatment success was defined as requirement of ≤ 1/day.

Results: A total of 61 patients were included in the study and each were cognitive intact (MMSE > 25). ICIQ-SF significantly improved in postoperative period ($p < 0.001$). PGI-I median score was 1 (1-4) in postoperative period. Success rate was 96.7% (n = 59) and 47 (77%) patients were complete dry. Revision requirement occured in 10 (16.4%) patients. When patient groups were compared according to the success and revision rates; presence of BMI > 25 kg/m2 was the only significant factor associated with revision requirement and there was no significant factor associated with success status.

Conclusion: AUS placement is a safe and effective method in the treatment of post-prostatectomy incontinence (PPI). Success and revision rates are similar regardless the etiology of PPI. Cognitive functions of patients may be crucial in the postoperative satisfaction status.

Keywords: Artificial urinary sphincter, post-prostatectomy incontinence, male incontinence

Stress urinary incontinence (SUI) may occur in men who underwent radical prostatectomy (RP) for the treatment of localized prostate cancer (Pca).In the literature, it was reported that 8% to 25% of the men were affected by persistent UI following RP [1-4]. Besides, as a more widespread procedure performed in urology practice, transurethral resection of the prostate (TUR-P) is associated with postoperative urinary incontinence range 1.8 to 5%. [5-8]. Although it is not a lethal complication, SUI following prostate surgery (RP or TUR-P)may impact the quality of life adversely and cause financial problems.Internal urethral sphincter deficiency is the main reason associated with SUI in men. Nowadays artificial urethral sphincter (AUS) placementis the standart treatment of moderate and severe postprostatectomy incontinence [9-11]. However,

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success of this system can be affected by many factors such as previous radiation therapy (RT), bladder neck or urethral stenosis, comorbidities of the patient and surgeon's experience. Additionally complications such as infection, urethral erosion, urethral atrophy and device malfunction may occur following the procedure. Although it is an effective treatment, the patients may be disappointed because of high expectations from the device. Patients should be informed about the device, the possible complications and the definition of success.

AUS placement has been performed in our clinic since 2008. In this study, we aimed to evaluate the patients who underwent AUS placement and report our results.

METHODS

In this retrospective study, the data of the patients who have undergone AUS placement (AMS 800) in our clinic since 2008 were evaluated. The patients with more than one year follow-up were included. The age, body-mass index, comorbidities, education level, previous RT history and urethral or bladder neck stenosis history of the patients were recorded. Cognitive status was examined using the Mini Mental Status Examination test (MMSE). International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) was completed in all patients before and 3 months after the treatment. The quality of life and satisfaction of the patients were evaluated using Patient Global Impression of Improvement (PGI-I) scalewhich is a transition scale that is a single question asking the patient to rate their urinary tract condition now,as compared with how it was prior to the treatment on a range from 1 (very much better) to 7 (very much worse).Filling these forms was a routine procedure as it was mandatory for preoperative decision-taking and postoperative follow-up. Number of pads used before and two months after the treatment were also recorded. Postoperative complications were assessed using Clavien-Dindo grading system [12]. Treatment success was defined as the requirement of maximum one pad per day. The patients who did not need any pad use were defined as complete dry. Additionally, to analyze the factors effecting success rate and revision rate, patients were grouped according to the age (≥ 65 years and < 65 years), BMI (≥ 25 kg/m^2 and < 25 kg/m^2), comorbidities, smoking habbit, previous RT history, education level (lower than high school - high school and above) and etiology of incontinence.

Urine culture was sterile in all cases in the operation day. Ceftriaxone 1 gr intravenous was administered to all patients prior to the surgery in the operating room. The perineal area was shaved in the operating room and washed with povidone-iodine for 10 minutes.

Surgical Technique

A diagnostic cystoscopy was performed prior the treatment in all cases. If an urethral or bladder neck stenosis were seen, they were treated and the treatment was delayed for two months. All the procedures were performed using a modifiedperineoscrotal vertical single incision by the same surgeon. Following the placement of urethral cuff, fascia transversalis was opened and dilated with finger. Following finger dilation, reservoir balloon was forwarded through the Retzius space. The connector tubes and control pump was placed in the scrotum. A 12 F Foley cathater was inserted during the procedure and removed in the postoperative day morning.All the patients were discharged in the postoperative day 1 and 7 days of amoxicillin/clavulanic acid 875/125 mg peroral BID was administered for each. The device was left deactivated for 6 weeks.

Statistical Analysis

Descriptive statistics for normally distributed continuous variables are reported as the mean ± standard deviation, with median (minimum–maximum) values calculated for non-normal distributions. Comparisons between groups were evaluated using the Fisher exact test for categorical variables and Wilcoxon test was used for continuous variables. The data was analyzed with IBM SPSS (version 20), and $p < 0.05$ was considered as significant.

RESULTS

From March 2008 to February 2017, a total of 66 patients who underwent AUS placement in our clinic

Table 1. Patient characteristics

Age (years)	69.69 ± 5.45
BMI (kg/m^2)	25.47 (22.28-31.53)
Diabetes Mellitus, n (%)	12 (19.7)
Hypertension, n (%)	23 (37.7)
Coronary Artery Disease, n (%)	13 (21.3)
Smoking, n (%)	20 (32.8)
Previous Radiotherapy, n (%)	7 (11.5)

were included in the study. Of the patients, 5 were lost to control and excluded. Patient demographics was shown in table 1.

All the patients completed MMSE and each were cognitive intact (MMSE > 25). The comparison of pre- and post-operative ICIQ-SF results of the patients was demonstrated in table 2. Questinnarie results significantly improved in the post-operative period ($p < 0.001$). Also, PGI-I median score was 1 (1-4) in the post-operative period (Table 2).

The success rate of the procedure was 96.7% (n = 59) and 47 (77 %) patients were complete dry. Any complications did not occur peroperatively. Revision requirement occured in 10 (16.4%) patients (Table 3). Skin extrusion of control pump and connector tubes occured in one patient. The vehicle was washed with antibiotic solution and povidone-iodine then scrotum skin was closed with suturation. Infection occurred in 2 patients and urethral erosionoccurred in 1 patient in the postoperative period. The device was removed and the revision was performed 3-6 months later. Urethral atrophy occured in 4 men and they were treated with tandem-cuff placement. Additionally, revision was performed due to the dysfunction of device in 2 men.

The comparisons of the patient groups according to the success rate and the revision rate were demonstrated in table 4. The presence of BMI ≥ 25 kg/m^2 was the only significant factor associated with revision requirement. There was no significant factor associated with success status.

Table 2. The comparsion of pre- and post-operative ICIQ-SF and median value of post-operative PGI-I

	Preoperative	Postoperative	*p* value
ICIQ-SF (median)	20 (17-21)	1 (0-20)	**< 0.001**
PGI-I (median)		1 (1-4)	

ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form ;PGI-I: Patient Global Impression of Improvement

Table 3. Revision requirements

Urethral erosion (n/%/CDc)	1/1.6/3b
Skin extrusion (n/%/CDc)	1/1.6/3b
Urethral atrophy (n/%/CDc)	4/6.5/3b
Device dysfunction (n/%/CDc)	2/3.2/3b
Infection (n/%/CDc)	2/3.2/3b

CDc = Clavien-Dindo classification

DISCUSSION

AUS, which was first described by Scott *et al*. [13] in 1973, is the standart tool for the treatment of post-prostatectomy incontinence (PPI). Initially, neurogenicurinary incontinence was the main indication for AUS placement. In time, with the increase of RP cases by the widespread use of prostate spesific antigen (PSA), PPI became the most frequent reason and the number of procedures increased dramatically. In the literature, there are various studies assessing the efficacy of the device, demonstrating success rates range from 61 to 100% [14]. In our study, compatibly with the literature, the success rate and complete dryness rate were 96.7% and 77.4%, respectively. To increase the success rate, the placement of 2 cuffs weredescribed by Kowalczyk *et al*. [15]. However as most urologists, we preferred tandem-cuff only for the cases who needed revision surgery because of urethral atrophy.

Previous RT is a major concern about the success

Table 4. Comparison of the patient groups according to the success rate and revision rate

	Success n (%) 59 (96.7)	*p value*	Revision n (%) 10 (16.4)	*p value*
Age (year)				
< 65	14 (100)	0.433	2 (14.3)	0.808
≥ 65	45 (95.7)		8 (17)	
BMI (kg/m^2)				
< 25	25 (100)	0.231	1 (4)	**0.029**
≥ 25	34 (94.4)		9 (25)	
DM				
No	48 (98)	0.273	8 (16.3)	0.977
Yes	11 (91.7)		2 (16.7)	
HT				
No	37 (97.4)	0.715	7 (18.4)	0.729
Yes	22 (95.7)		3 (13)	
CAD				
No	47 (97.7)	0.314	8 (16.7)	0.912
Yes	12 (92.3)		2 (15.4)	
Previous RT				
No	52 (96.3)	0.605	10 (18.5)	0.748
Yes	7 (100)		1 (14.3)	
Education level				
Low	24 (96)	0.792	5 (20)	0.526
High	35 (97.2)		5 (13.9)	
Smoking				
No	41 (100)	0.104	2 (10)	0.346
Yes	18 (90)		8 (19.5)	
Etiology of PPI				
RP	43 (97.7)	0.483	9 (20.5)	0.168
TUR-P	16 (94.1)		1 (5.9)	

BMI = Body-mass index, DM = Diabetes mellitus, HT = Hypertension, CAD = Coronary artery disease, RT = Radiotherapy, PPI = Post-prostatectomy incontinence, RP = Radical prostatectomy, TUR-P = Transurethral resection of prostate

of device and complications. RT may decrease vascularity and increase fibrosis in bulbar urethra. Therefore it was speculated that, prior radiation therapy increases the risk of urethral atrophy and may increase the chance of cuff erosion [16]. Also in the consensus of the International Continence Society, RT was revealed as a factor which predisposes complications [17]. There are contoversial results in the literature. In the study performed by Ravier *et al*. [18], there was no statistically significant difference in continence status between irradiated and non-irradiated group. However, patients with prior RT were more prone to infection and explantation [18]. In another study, similar social continence rates and

complication rates were demonstrated in two groups [19]. In our cohort, 7 patients were irradiated prior to the surgery and success rate of this group was 100%. Also only one patient needed revision due to the mechanical dysfunction 5 years after the surgery. Regarding our limited data, previous RT should not be a concern for the treatment.

Infection following AUS placement is a devastating problem. As any prosthetic device, AUS is prone to infection. In the literature, infection rates range from 1 % to 8 % [20-23]. In the management, the device is removed and revision is performed after 3 months or more. It was revealed that a new device may be implanted with similar success rates [24]. In 2007, AMS presented InhibiZone-coated (rifampin and minocycline hydrochloride coating) AUS to reduce infection rate, however in the study performed by de Cogain *et al*. [20], it was revealed that antibiotic coating did not impact the infection rate and increased the cost of the device. Infection is commonly associated with urethral erosion. In our study, infection rate was 3.2 % (2 patients), however in our infected patients urethral erosion did not occur. In the study performed by Bryan *et al*. [25], immediate replacement for the infected patients without erosion was revealed as a valid option. We preferred the classic management as we think it is safer. Of the patients, 1 was completely dry and 1 was incontinent following the revision.

The periurethral tissue should be protected during dissection to avoid the erosion after the procedure. Erosion rates in contemporary series range from 2-15 % [14, 19, 26, 27]. Erosion in the early period is commonly associated with unrecognized injury, in the late periodis with iatrogenic reasons. In our study, erosion occured in only 1 patient due to the urethral cathaterization in emergency service 2 years after the surgery. Subsequent to the unsuccessful cathaterization trial in emergecy service, suprapubic cathaterization was performed by us. Management of the urethral erosion is not clear. To remove only the cuffinstead of the whole device in the non-infected cases is the primary suggestion. We removed the whole device and performed urethroplasty. Following the revision (4 months later), continence was not achieved. This was related with the urethral atrophy due to the damaged tissue vascularization.

A disadvantage of AUS is the periodic revision requirement of the device. In the study performed by Linder *et al*. [10], of 1082 patients, 338 were undergone revision surgery due to the infection or erosion, device malfunction, urethral atrophy and pump malposition or tubing complications. They reported AUS survival rate of 90% at 1 year, 74% at 5 years, 57% at 10 years and 41% at 15 years [10]. Urethral atrophy is the most frequent indication of revision in long term follow-up. Itis associated with continuous pressure on the tissue and damaged vascularization of the area and causes increased incontinence. Down-sizing the cuff and increasing fluid in the system are treatment choices, however we prefer to implant a tandem cuff. In our cohort, atrophy occured in four patients and the revision procedure was successful in all cases. Additionally; as any prosthetic device, mechanical dysfunction can occur in AUS. Linder *et al*. [10], revealed that to replace the whole device instead of the dysfunctioning part achieved better results. In our clinical practice, we prefer to replace the whole device and continence was achieved in two patients who underwent revision surgery due to the device malfunction.

The AUS remains the most effective long-term surgical treatment for SUI in men. Despite to the high success rate, it is not suitable for some patients. To be able to use this mechanic device, a sufficient intelligence level and dexterity is an important requirement. Considering this; since AUS placement was first performed in our clinic, all the patients have completed MMSE test prior to the surgery. As far as we know, there is not any study assessing the preoperative cognitive status of the patients. In the current study, the patients completed MMSE prior to the surgery. We believe that to obey the directives and correctly use of this device may cause more satisfactory results and a longer device life. Perhaps as a result of all the patients' being cognitive intact (MMSE > 25), satisfaction rate was prominently high [PGI-I median= 1 (1-4)] in our study.

To our knowledge, there is not a study assessing the outcomes of the AUS placement according to the etiology of PPI. In this study, we divided the patients into two groups as those who had undergone TUR-P and those who had undergone RP. Any statistically significant difference was not observed between the success and revision rates when groups were compared. However, the number of patients was low

and further studies should be performed.

As known,the incidence of chronic diseases increases by the ageing [28]. In the literature, the number of the studies evaluating the outcomes of AUS placement in elderly males is lacking. Also controversial results were revealed. In the study performed by O'Connor *et al*. [29], age of the patient was not defined as a factor which adversely effects the outcomes of the procedure. However, Ziegelmann *et al*. [30] reported that older males were significantly more likely to experience device infection/erosion compared with younger patients. In the current study, presence of comorbidities and age ≥ 65 years were not associated with success of the operation or revision requirements. We think that AUS placement can be safely performed in elderly patients.

Limitations

There are some limitations of this study. First,it was a retrospective non-randomized design. The data such as detailed pathology results of the patients, length of incontinence period prior to the surgery, the medications used, could not be evaluated. Second, the number of patients was relatively low. Third, it was a single center and single surgeon study, which may limit generalizability.

CONCLUSION

The AUS placement is a safe and effective method in the treatment of SUI in men regardless the patient's age. Patient counseling about the definition of success and periodic revision requirement is important prior to the surgery. The success and revision rates are similar regardless the etiology of incontinence (TUR-P or RP). The patients who are cognitive intact and who have sufficient dexterity may be more satisfied from the device.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Does circumcision change uroflowmetry parameters?

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ABSTRACT

Objectives: The benefits of circumcision, which is one of the most frequently performed surgical procedures, are controversial. In our study, before and after circumcision, uroflowmetry parameters were compared to evaluate the effects of circumcision on voiding.

Methods: Children between the ages of 5-15 years who applied to the outpatient clinic for voluntary circumcision and who did not have underlying diseases and voiding problems were included in the study. Circumcision was performed by specialist in sterile conditions under general anesthesia. Uroflowmetry was evaluated by voiding volume, voiding time, maximum flow rate, average flow rate, shape of the curve. The pre-circumcision and post-circumcision uroflowmetry results were compared statistically.

Results: Fifty patients with a median age of seven years (range: 5-10 years) were included in the study. When uroflow parameters were compared in our study, the maximum flow rate, mean flow rate and the time to maximum flow rate were found significantly different ($p < 0.05$). The plateau pattern was detected in 30% of patients before circumcision, while in 8% of patients after circumcision.

Conclusions: Circumcision performed by specialists under sterile conditions has positive effects on uroflow parameters.

Keywords: Male circumcision, uroflowmetry, children

Circumcision is the surgical removal of the prepuce, either in whole or in part. It is one of the most practiced surgical procedures in the world. There is no standardization regarding the surgical technique. Today, the debate continues with regard to the usefulness of the practice of circumcision. In the literature, there are publications that set forth opposing views about its practice due to the fact that foreskin protects the penis tip with both mechanical and secreted substances and because of its functional importance in orgasm in sexual life due to the presence of many sensory receptors. However, there are also studies showing that the practice of circumcision is beneficial in children who have frequent urinary tract infections and that this practice has a protective role in sexually transmitted diseases such as AIDS [1-3].

As a result, circumcision is a surgical procedure that is very frequently practiced based on religious beliefs, traditional reasons or medical reasons. A series from the year 2010 states that there is no systematic study comparing circumcised men and uncircumcised men [4]. The effect of circumcision on voiding dynamics in children or adults is still an unknown issue.

Uroflowmetry is an easy-to-apply, non-invasive test in which voiding is evaluated. Uroflowmetry can

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be used to assess the effect of circumcision on urine flow. In our study, it was aimed to investigate the effects of circumcision on uroflowmetry parameters.

METHODS

Upon the approval by the local ethics committee, children between the ages of 5-15 years were enrolled, who applied to the outpatient clinic for voluntary circumcision and who had no underlying disease and voiding problems. There was no phimosis pre-circumcision. After obtaining consent from their families, uroflowmetry was performed before circumcision. Circumcision was performed under general anesthesia by the surgical circumcision method. In the circumcision, the preputium was removed in a way that approximately 0.5 cm of preputium remained on the side of the glans, without performing frenulum excision. After excision, the glans-skin flap was repaired with individual sutures with 5/0 Rapid Vicryl. On the first day, closed dressings were made, and the dressing was opened one day later, and povidone-iodine was recommended to be applied twice a day. After one-day hospitalization, oral analgesics and anti-inflammatory medication (Ibuprofen 5 mg/kg, 3×1, daily) were started and the patient was discharged. Bathing was recommended two days later, along with an outpatient visit one week later for incision control. An outpatient visit was recommended one month after circumcision for voiding control, and post-circumcision uroflowmetry was performed at this control.

The uroflowmetry was assessed based on voided volume, flow time, maximum flow rate, avarage flow rate, and the shape of the curve. Voided volume was excluded in children under 50 cc [5]. The expected bladder capacity was calculated as 30 + (age × 30) mL [6]. The shape of the curve was evaluated as bell-shaped, tower, staccato, intermittent and plateau as recommended by the International Children's Continence Society ICCS [7, 8]. Pre-circumcision and post-circumcision uroflowmetry results were compared statistically.

Statistical Analysis

Data were evaluated using SPSS 13.0 program. A comparison of uroflow curves was carried out using the chi-square test. Wilcoxon test was used with the evaluation of uroflow parameters. A *p*-value of less than < 0.05 was considered statistically significant.

RESULTS

The median age of 50 patients included in the study is 7 years (5-10 years). In the pre-circumcision uroflow examination, 35 (70%) patients had a normal voiding curve, whereas a plateau voiding pattern was detected in 15 (30%) patients. While the plateau voiding pattern continues in 4 (8%) patients post-circumcision, the voiding pattern is normal in 46 (92%) patients. The change of voiding pattern before and after circumcision is statistically significant (p = 0.001).

Median flow time before circumcision is 16.34 ± 1.43 seconds, and 15.36 ± 1.65 seconds after circumcision. The flow time is the same before and after circumcision (p = 0.24). The maximum flow rate median before circumcision is 14.36 ± 1.65 mL (range: 9-28 mL) and 15.84 ± 0.70 mL after circumcision. Maximum flow rate increased after

Table 1. Uroflowmetry parameters by precircumcision and postcircumcision

Parameters	Pre-circumcision	Post-circumcision	*p* Value
Voided volume (mL)	175.5 ± 96	197.38 ± 118	**0.031**
Qmax (mL/sec)	14,36 ±1.65	15,84±0.70	**0.01**
Qavg (mL/sec)	10.96 ± 0.42	12.32 ± 0.41	**0.01**
Time to Qmax (sec)	15.87 ± 0.71	10.96 ± 0.96	**0.002**
Flow time (sec)	16.34 ± 1.43	15.36 ± 1.65	0.24

Data are shown as mean ± standard deviation. Bold marked data is statistically significant. Qmax = maximum flow rate, Qavg = average flow rate

circumcision ($p = 0.01$). The median time to maximum flow before circumcision is 15.87 ± 0.71 seconds, after which, this time is 10.96 ± 0.96 seconds. Time to maximum flow decreased after circumcision ($p = 0.002$). The avarage flow rate before circumcision was 10.96 ± 0.42 seconds, after which, the avarage was 12.32 ± 0.41 seconds. An increase was detected in the avarage flow rate after circumcision ($p = 0.01$). The amount of voided volume was 175.5 ± 96 cc before circumcision, after which, this was measured as 197.38 ± 118 cc. An increase was observed in the amount of voided volume after circumcision ($p = 0.031$). Uroflowmetry parameters by pre-circumcision and post-circumcision are shown in Table 1.

DISCUSSION

Circumcision is one of the most practiced surgical applications worldwide. Although it differs between societies, one in every 3 men worldwide is circumcised [9]. Bleeding and infection have been reported most frequently in several epidemiological studies evaluating post-circumcision complications [4]. The complication rate is determined by the expertise of the person who performed the circumcision and the environment in which the procedure was performed. Serious complications are not observed in sterile environments and in circumcisions performed by specialists [4, 10]. Although there are studies on surgical complications, no study evaluating the functional results of circumcision has been found. Uroflow is an easy-to-apply, noninvasive method in which voiding is evaluated objectively. In our study, the functional results of circumcision were discussed by evaluating the pre-circumcision and post-circumcision uroflowmetry parameters.

Circumcision is performed for religious, cultural and medical reasons [4]. In all patients included in our study, circumcision was performed for religious and cultural reasons. There was no complaint to suggest voiding dysfunction in any of the patients. Although there were no complaints, 15 (30%) patients had obstructive voiding pattern before circumcision. After circumcision, the obstructive voiding pattern was detected in 4 (8%) patients. This result was interpreted to suggest that circumcision had a positive effect on urine flow. Since the obstructive pattern before circumcision is high, this suggests that prepuce can change the voiding pattern in children who do not have voiding problems. The significant improvement of the obstructive pattern after circumcision in the same children shows that circumcision has positive effects on urine flow. In a study conducted in healthy children in Spain, the bell-shaped curve, which is considered as the normal flow pattern, was seen in more than 90% of both genders [11]. In the same study, the plateau curve was observed in 5.2% in boys, but not in 9 to 14-year-old girls [11]. The anatomical difference of the urethra in men may be the cause of this obstructive pattern. In addition, no information was provided about whether the children with the obstructive pattern were circumcised or uncircumcised. In addition to urethral factors in the obstructive pattern in uroflow, the presence of preputium may contribute. It should also be remembered when making an assessment for voiding dysfunction that the foreskin may cause this pattern in children with obstructive voiding patterns. Clinical guidance should not be provided by evaluating the curve alone.

When uroflow parameters were compared in our study, the maximum flow rate, avarage flow rate and the time to maximum flow rate were found different. These results support the positive effects of circumcision on uroflow and voiding. In our study, post-circumcision uroflow assessment was performed in the early postoperative period. Late-term control uroflow assessments will allow for the comparison of the effects of circumcision on long-term uroflow.

Voiding problems and obstructive patterns observed after circumcision, which were not present before circumcision, are mostly related to meatal stenosis. In our study, there was no voiding problem in the first month after the circumcision evaluation. Meatal stenosis has also not been detected. All circumcisions were performed by a specialist in a sterile operating room environment under general anesthesia. Meatal stenosis is more commonly observed in circumcisions performed during the newborn and infant period [12, 13]. The children included in our study are children over 5 years old. The prediction that performing circumcision under suitable conditions and age range may prevent the development of meatal stenosis was also supported by this study.

CONCLUSION

Circumcision has positive effects on uroflow parameters and voiding. Circumcision performed by specialists in the appropriate age range in sterile environments has positive results in terms of voiding physiology.

Authors' contributions

SS = Design of research, data collection and analysis, preparation of article and revisions; **EAKE** = Data analysis, preparation of article and revisions .

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2020;6(4):287-291 Original Article

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Retrospective evaluation of indications and birth results of cesarean section due to ophthalmologic diseases

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ABSTRACT

Objectives: To investigate the outcomes of cesarean section due to ophthalmologic indications.

Methods: This retrospective clinical study included 40,190 patients underwent cesarean section due to ophthalmological indications between January 2013 – August 2015 in MLP Care Group Hospitals (It includes 32 hospitals). Demographic data, ophthalmologic history and indications and surgical outcomes of caesarean section was assessed.

Results: Of the 53 patients with caesarean delivery due to ophthalmologic indications, 32 (60.4%) had high degree myopia, 7 (13.2%) had degenerative myopia, 8 (15.1%) had history of ocular surgery, 2 (3.8%) had history of vitreoretinal surgery due to retinal detachment, 2 (3.8%) had glaucoma with uncontrolled intraocular pressure, 1 (1.9%) had retinitis pigmentosa and 1 (1.9%) had optic neuritis.

Conclusions: Ratio of ophthalmic indications is small within all cesarean indications and further longitudinal studies are needed to prevent from unnecessary cesarean section.

Keywords: cesarean section, myopia, retinal detachment

Number of birth deliveries with cesareansection is rapidly increasing globally and in Turkey. Based on the data of the World Health Organization, number of deliveries with cesarean section had increased by 48.9% between the years 1992 and 2007 [1]. Likewise, while the rate of births with cesarean section was 21% in Turkey in 2002, it increased to 47% in 2011 [2]. This means that 750,000 births with cesarean section occurs in the average each year in our country [3]. Although the reasons for preferring birth with cesarean section are commonly obstetric reasons such as repeat sections or fetal distress, the need for cesarean section can also arise with non-obstetric reasons [4]. Puzio *et al*. [5] have reported that 17% of cesarean section indications are related to non-obstetric reasons and 20.5% of non-obstetric reasons are ophthalmologic diseases.

Together with the several physiologic and pathologic effects of pregnancy on the eye, it can cause the deterioration of the course of existing ophthalmologic diseases [6]. It has been reported in the literature that diseases capable of leading to serious ocular morbidity including retinal detachment, central serous chorioretinopathy, pregnancy-related hypertensive retinopathy, papilledema, obstructions of retinal artery and vein and diabetic retinopathy can occur during pregnancy or their courses can deteriorate. In their study on 4895 pregnant women, Socha *et al*. [7] reported that 2.04% of indications of cesarean sections performed were ocular diseases. Furthermore, it has been stated that ocular diseases that are the most common cesarean indications are myopia, retinopathy and

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glaucoma [7].

Review of the literature shows that there is no consensus on planning the mode of delivery based on ocular diseases [6, 8, 9]. Furthermore, although this is an inter-disciplinary issue, number of studies that ophthalmologists and obstetricians work together on this issue is rather small. In our study, we aimed at evaluation of the effects of ophthalmologic diseases on the decision for the delivery mode in Turkey, and to carry out an inter-disciplinary evaluation.

METHODS

Pregnant women who delivered their babies with elective cesarean section in MLP Care Group Hospitals (It includes 32 hospitals) with indications related to ophthalmologic diseases between January 2013 and August 2015 were included in this retrospective study. The study was carried out after obtaining the approval of the ethical committee of MLP Care Group Hospitals (It includes 32 hospitals), Ankara (Number:2019/002).

Pre- and post-delivery ophthalmologic findings of all the pregnant women, for whom elective cesarean section was performed with ophthalmologic indications, were investigated from the records of their examination and ocular pathologies creating cesarean indication were recorded. Age, weight, length and body mass index (BMI) were noted. Gestational age, birth weight of the newborns were also noted. All the data required for the study were collected from the patient files after the patients were discharged. Reliability of information was secured through crosswise checks on anesthesia, nursing and obstetric reports.

Full ophthalmologic examinations were carried out on all the patients before the procedure. Visual acuity was determined using the Snellen scale. Intraocular pressure measurements were carried out with noncontact tonometry (CT-80 Tonometer, Topcon, Japan), and Goldmann applanation tonometry was used to repeat the managements for results exceeding 21 mmHg. Macula, optic disk and peripheral retinal examination was carried out with the help of Goldmann 3-mirror lens after dilation of the pupils and topical anesthesia. Optic coherence tomography and fundal fluorescence angiography were performed if needed. Patients with high myopia, degenerative myopia, history of retinal detachment, history of ocular surgery, retinitis pigmentosa and history of optic neuritis did not receive any treatment unless there was an associated complication. Only patients with glaucoma attended scheduled control visits before and after cesarean section for medical management.

Statistical Analysis

Statistical Package for the Social Science (SPSS Version 22.0, Armonk, NY: IBM Corp) software were used to analyze the study outcomes. The normal distribution assumption of the data was tested by the Shapiro-Wilk test. Frequencies of the variables were calculated. A p value < 0.05 was considered as significant.

RESULTS

Fifty-three pregnant women that gave birth with cesarean section because of ocular diseases out of 40,190 that gave birth with cesarean section between the above mentioned dates were included in the study. Rate of pregnant women, for whom cesarean section was performed because of ocular diseases was calculated as 0.13%. In this study, the mean age was 26.75 ± 5.08 years and the mean BMI was 29.75 ± 5.08 kg/m^2. Demographic characteristics of patients

Table 1. Demographic data of the patients

	Minimum	Maximum	Mean	Std. Deviation
Age (years)	18	38	26.75	5.08
Length (cm)	145	185	161.96	6.55
Weight (kg)	55	112	77.32	13.30
BMI (kg/m^2)	20.2	44.2	29.75	5.51

Table 2. Distribution of indications based on ocular diseases in patients, for whom cesarean section was performed

	Ophthalmic Disorders (n = 53)	Cesarean indications (n = 40,190)
High Myopia (n = 32)	60.4%	0.079%
Degenerative Myopia (n = 7)	13.2%	0.017%
Retinal Detachment (n = 2)	3.8%	0.004%
Previous Ocular Surgery (n = 8)	15.1%	0.019%
Uncontrolled Glaucoma (n = 2)	3.8%	0.004%
Retinitis Pigmentosa (n = 1)	1.9%	0.002%
Optic Neuritis (n = 1)	1.9%	0.002%

are given in Table 1.

Gestational diabetes was found in 1 (1.9%) of the patients, who participated in the study, hypertension accompanying gestational diabetes in 1 (1.9%), type 2 diabetes mellitus in 1 (1.9%), pregnancy cholestasis was found in 1 (1.9%) and epilepsy was found in 1 (1.9%) of the patients who participated in the study. However, lack of any effects of pregnancy on these diseases was confirmed by the ophthalmologist.

Of the 53 pregnant women, for whom cesarean section was performed because of ophthalmic disorders, 32 (60.4%) had high myopia, 7 (13.2%) had degenerative myopia, 2 (3.8%) had past retinal detachment, 8 (15.1%) had past ocular operations, 2 (3.8%) had uncontrolled glaucoma, 1 (1.9%) had retinitis pigmentosa and 1 (1.9%) had optic neuritis. No changes were observed in their findings related to their respective ophthalmologic disease in the examination carried out at month 1 following delivery. No ocular complication associated with cesarean section was observed 1 moth after the cesarean section.

Of the 52 newborns who were given birth through cesarean section, mean birth weight was 3,281 ± 438 grams, gestational age was 38.3 ± 0.7 weeks and mean RDS was observed in 2 (3.8%), wet lung and hypoglycemia in 1 (1.9%), patent foremen ovale in 1 (1.9) and neonatal icterus was observed in 1 (1.9%).

DISCUSSION

There is no consensus between obstetricians or between ophthalmologists as regards whether or not ophthalmologic diseases are indications for cesarean section. Chiu *et al*. [8] have reported that 34% of obstetricians recommend delivery with cesarean section in pregnant women with retinal detachment risk, while 4% of ophthalmologists recommend it for the same condition. Recommendation of cesarean section by 26% of ophthalmologist in the same study in pregnant women who had been treated because of retinal detachment while Inglesby *et al*. [10] had stated that past retinal detachment surgery is a contra-indication for vaginal delivery shows that there is no consensus in this issue even between ophthalmologists, cesarean section was performed on only 2 patients because of retinal detachment. Furthermore, we are unable to carry out a statistical comparison with the reason that there were not patients with retinal detachment who had vaginal delivery. This is the most important limitation of our study.

In their study on 4,895 pregnant women, Socha *et al*. [7] reported that 2.04% of cesarean section indications were ocular diseases. This ratio was calculated as 0.13% in our study. We consider this ratio somehow too small based on the fact that cesarean section rates with obstetric causes are rather high in our country. However, statements based on net numbers require larger studies. It was stated in the same study that ocular diseases constituting the most frequent cesarean indications include myopia, retinopathy and glaucoma. These results are similar with ours.

Psenkova *et al*. [11] showed that number cesarean

operations with non-obstetric indications significantly reduced after training of obstetricians on non-obstetric cesarean section indications. These data reported in the literature indicate that more studies are required on the issue of how the ophthalmologic diseases affect the mode of delivery, and training on this issue is required for the relevant specialty areas.

It is thought that the acute increase in intraocular pressure and decrease in ocular perfusion related to the valsalva maneuver during vaginal delivery can cause optic nerve damage in glaucoma patients [12]. Cesarean section is recommended for patients with high grades of myopia or retinal degeneration based on the thought that vaginal delivery can trigger retinal detachment [13, 14]. In the studies of Socha*et al*. and in our study, the most frequent cesarean indications are myopia and retinaldetachment. However, there are no evident-based reports in the literature indicating that vaginal delivery is associated with retinal detachment or progression of glaucoma [13, 14]. Animal experiments, observational and comparative studies covering the pre- and post-delivery periods in pregnant individuals with ophthalmologic diseases are required.

To our knowledge, neither a gynecologist, nor an ophthalmologist can decide cesarean section due to an ophthalmologic indication. Mohammadi *et al*. [15] emphasized that all gynecologist expressed the need of ophthalmologist's suggestion for cesarean section due to ophthalmologic indications. There is no guideline in management of pregnant patients with ocular disorders; therefore, it should be a mutual decision of both gynecologists and ophthalmologists as it was in the present study.

CONCLUSION

In conclusion, ophthalmologic concerns direct both gynecologists and ophthalmologists to cesarean section. Although ratio of ophthalmic indications is small within all cesarean indications, further longitudinal studies are needed to prevent from unnecessary cesarean section.

Conflict of interest

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Improvement of the functional recovery of the upper limb in hemiplegic patients by the use of the technique of induced stress therapy

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ABSTRACT

Objectives: To investigate the effects of the induced stress therapy technique in functional recovery of the upper limb in hemiplegic patients.

Methods: We conducted a longitudinal study that consisted in following the evolution of the functional recovery of the upper limbs of 60 hemiplegic subjects of the center for physical disabilities of Kinshasa subjected to a program of induced stress therapy for a period of six months from April 2018 to October 2018. The Fugl Meyer scale and Action Research Arm test allowed us to see the effects of this treatment. The parametric t test of student allowed us to compare the averages before and after the treatment.

Results: After 6 months of the study, the results of our cases showed a very significant difference between the mean values of global motor skills scores at Action Research Arm between the beginning (51 ± 21%) and the end of treatment (64 ± 20%; $p < 0.05$). The difference in mean values at the Fugl Meyer scale was also very significant, both at overall scores and under-scores ($p < 0.05$). There is a very significant difference between older and younger patients compared to the mean values of their overall scores on the motor and independence scales ($p < 0.05$).

Conclusions: We found that induced stress therapy significantly improved the level of functional recovery and autonomy at the Action Research Arm and Fugl Meyer scales. In addition, this improvement was a little slower in the hand than in the other segments of the upper limb.

Keywords: induced stress therapy, functional recovery, hemiplegic, upper limb

Hemiplegia corresponds to an engine deficit linked to an impairment of the central nervous system [1]. Because of the path of the motor path and its decussating at the level of the bulbar pyramid, hemiplegia affects, in the majority of cases, the hemi-body opposite the injured cerebral hemisphere and according to the extent and location of the brain lesion, it may affect the upper limb and the face or lower limb more [1].

Person [2] reported that 80% of hemiplegic pa-

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tients recover walking, while only 28 to 57% recover the grip [3, 4]. Delden also came to a similar conclusion as he thinks that 80% of hemiplegics have severe upper limb involvement, and that only 30 to 40% recover useful grasping [2].

Although it is the severity of the cerebral involvement which conditions the degree of motor and functional recovery [2], other factors are also decisive, including those related to the rehabilitation treatment, and which are related to its precocity, its repetitiveness and its active character.

In the Democratic Republic of Congo, we have observed that most hemiplegic patients find it very difficult to recover the functionality of their upper limbs after the rehabilitation sessions. Since stress-induced therapy has been scientifically proven in functional recovery of the upper limbs, it is less used by rehabilitation professionals in Kinshasa. In addition, we have hardly found enough studies focused on upper limb rehabilitation.

Nevertheless, Bofosa *et al*. [5] conducted a study in our community, on the impact of induced stress therapy (IST) comparing two groups of patients, ie., those subjected to IST and a control group, but not have not studied the influence of sex, age and duration of disease in functional recovery after IST. The objective of this study is to evaluate the effects of stress therapy in hemiplegic subjects taking into account the sex, age and duration of the disease.

METHODS

Nature and Period of Study

We conducted a cross-sectional experimental study that tracked the evolution of upper limb functional recovery in hemiplegic subjects undergoing a stress-induced therapy program over a six-month period from April 2018 to October 2018.

Framework of the Study

We conducted the present experimental study in the rehabilitation center for physical disabilities of Kinshasa in the Democratic Republic of Congo.

The choice of this framework is justified: (a) Primo: he is renowned in the field of rehabilitation in Kinshasa; (b) Secondly, it has a large number of hemiplegic patients frequent; (c) Tertio: the regularity of hemiplegic patients at re-education sessions.

Population of the Study

The study was approved by the Ethics Committee of the Departement of Physical medicine and rehabilitation (Democratic Republic of Congo) (Number: A00-987 50) and was registered on the Clinical Trials Gov. Registry, with the number NCT 05860022 (12 Febuary 2018). All experiments were performed in accordance with relevant guidelines and regulations. Each hemiplegic subjects received information about the purpose and nature of the protocol. After reading and understanding the information, a statement at testing to informed consent was approved, obtained and signed by the hemiplegic subjects. This study consisted of a population of hemiplegic patients attending Kinshasa physical rehabilitation center.

Criteria

The following inclusion criteria were selected for this study: (a) To be a hemiplegic patient regularly followed at the rehabilitation center for the physically handicapped; (b) Have a card and a complete medical file; (c) Have an average age between 20 years and over; (d) To have freely consented to participate in this study; and (e) Have already followed more than 24 sessions. All patients who did not meet the inclusion criteria mentioned above were excluded.

Sample

A convenience sample of 60 hemiplegic patients from the rehabilitation center for disabled people. We divided these patients according to: sex (to realize the effect of sex on this recovery); age: to reveal the influence of age on the functional recovery of the upper limbs and the duration of the disease to see the effect of this time on this recovery.

Scale and Test Used

The Fugl Meyer scale allowed us to evaluate upper extremity motor skills in hemiplegic patients. Thanks to this scale, we measured the motor skills at the level of the shoulder; elbow and forearm. All tests were scored from 0 to 2 (0: not done, 1: partially done, 2: totally done).

Action Research Arm Test (ARA), this test allowed us to measure the fine motor skills of the

upper limbs of hemiplegic patients. It consists of four items: grab, hold, pinch and global movements. It has been rated 0-3 (0: Can not perform any part of the test; 1: Can perform part of the test; 2: Can perform the test but in abnormally long time or with great difficulty; Execute the test normally).

Intervention Program

The principles of the treatment consisted of: (a) respecting the fatigability of the patient; (b) fight against spasticity and avoid strengthening it; (c) fight against syncinesia; (d) adapt the exercises to the patient's abilities; and (e) let the patient do his own activities of daily living (ADL) within the limits of his abilities. The healthy limb being immobilized by an immobilization vest, an immobilization scarf or a velpo band, and the patient had to perform the different tasks or activities of daily life with the sick member. Different objects and toys were used to perform various tasks such as showering, combing hair, eating, writing, moving an object, etc. We also used other exercises involving the cognitive abilities of the patient (concentration, memorization, intention of movement), using different objects (hoops, pads, rings) and their characteristics (shape, size, color, weight), and adapting the instruction to obtain a movement allowing the stretching of the spastic muscle.

Ethical Consideration

All participants had consented to write to participate in the study according to the Helsinki Declarations. The information collected from participants was kept confidential. All authors declare originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the Authors responsibilities. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

Statistical Analysis

Data from this study were captured on Microsoft Excel 2010 software and exported to SPSS software version 20.0 for Windows. We presented the results in the tables and figures as means, standard deviation, and percentage. To appreciate the effects of induced stress therapy on upper limb functionality, we used the student's parametric t test. We compared the averages by age, sex and duration of illness.

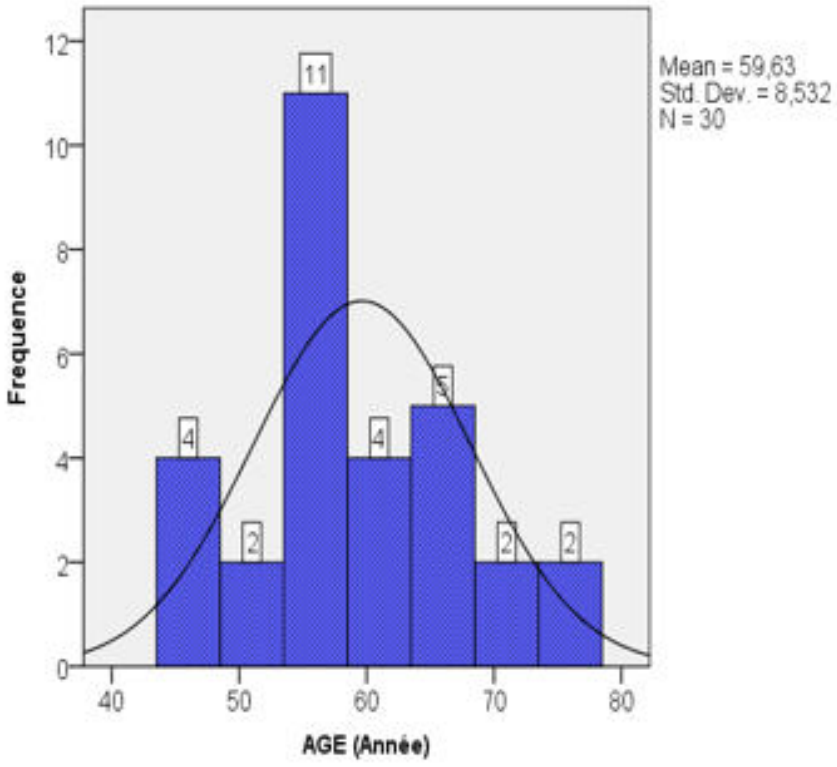

Fig. 1. Distribution of patients by age.

RESULTS

Mean age of the patients was 59.6 ± 8.5 years, with extremes of 43 years and 79 years (Fig. 1). In this study, 63.3% of patients were men and 36.7% were women (Fig. 2).

There were 21 (70%) ischemic strokes and 9 (30) hemorragic strokes; the sign of laterality concerned the left hemi-body in 60% of cases 8 Table 1). These patients were in 53.3% of cases between 6 and 11 months of the disease, and 46.7% at least 12 months. In analysis of the influence of the program, there was a very significant difference in the mean values of the overall motor mobility scores at the ARA between the onset (51 ± 21%) and the end of the treatment (64 ± 20%), with a $p = 0.000$; on the other hand, the analysis of the sub-scores did not show any significant difference in pinching (initially 3/18 and 4/18 at the end) and global movements (5/9 initially and 6/9 at the end), with a $p > 0.05$ (Table 2). The difference in mean values at the Fugl Meyer scale was also very significant, both at the global scores and under the scores ($p = 0.001$).

Table 3 shows that the mean values of the overall ARA and Fugl Meyer scores showed no significant difference between patients who were less than 12 months and those who were more or less 12 months ($p > 0.05$). The same is true for the comparison of the mean values of the overall ARA and Fugl Meyer scores by sex, which also did not show a significant difference between men and women ($p > 0.05$) (Table 4). There was a significant difference between elderly and younger patients compared to the average values of their overall scores ($p < 0.05$) (Table 5).

Table 1. Distribution of patients by type of stroke, hemiplegic hemi body and duration of illness

Parameters	n	%
Type of stoke		
Ischemic	21	70.0
Hemorrhagic	9	30.0
Hemicorps reached		
Left	18	60.0
Right	12	40.0
Duratıon of disease (months)		
6 – 11	16	53.3
12 – 24	14	46.7

DISCUSSION

This study involved 30 patients undergoing

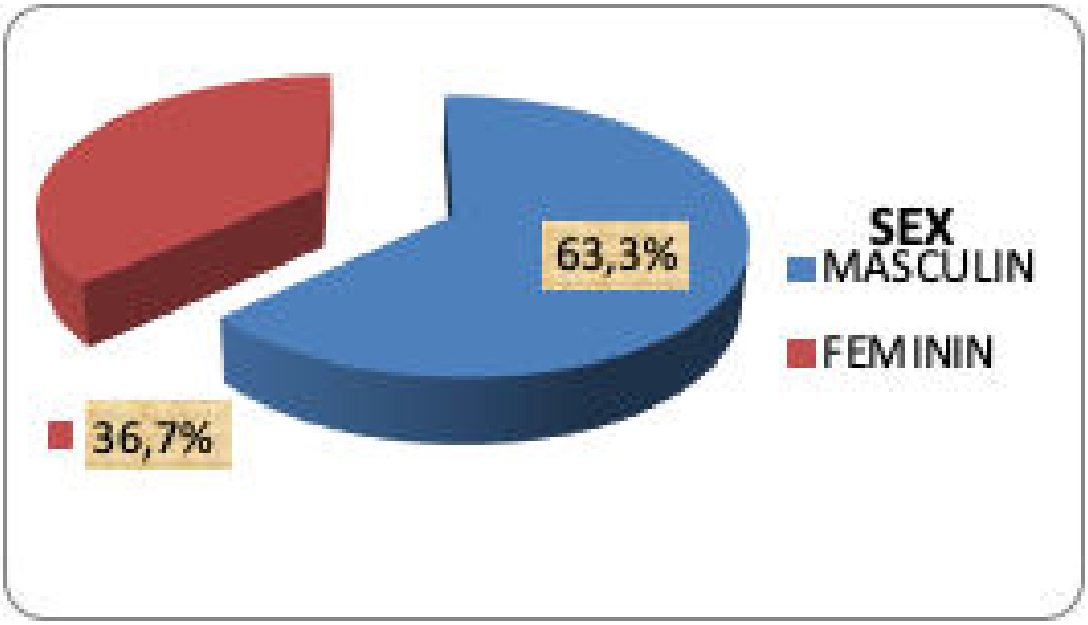

Fig. 2. Distribution of patients by gender.

Table 2. Presentation of the functional and autonomy profile at the ARA and Fugl Meyer scales

Parameters	Before	After	t	*p* value
% Global Ssore ARA	51 ± 21	64 ± 20	-8.901	**0.002**
Under scores ARA				
Enter /18	9 ± 4	12 ± 4	-7.129	**0.001**
Hold /12	7 ± 3	9 ± 3	-6.567	**0,001**
Pinch /18	3 ± 2	4 ± 2	1.32	0.06
Global Movements /9	5 ± 1	6 ± 1	1.34	0.06
% of score global Fugl Meyer	50 ± 21	65 ± 17	-7.5	**0.003**
Under Fugl Meyer scores				
Shoulder/elbow/arm/30	16 ± 7	20 ± 5	-6.8	**0.006**
Wrist /10	5 ± 2	7 ± 2	-7.24	**0.001**
Hand /14	6 ± 3	8 ± 3	-4.75	**0.001**
Coordination-speed /6	3 ± 2	4 ± 1	-7.21	**0.001**

Data are shown mean ± Standard deviation. ARA = Action Research Arm

Table 3. Presentation of the mean values of initial and end-of-treatment global functional and autonomy scores as a function of duration of illness

Parameters		Duration of disease		t	*p* value
		< 12 Month	≥ 12 Month		
% ARA	Before	50 ± 23	53 ± 20	-0.370	0.710
	After	62 ± 23	66 ± 17	-0.55	0.58
% Fugl Meyer	Before	50 ± 23	51 ± 20	-0.200	0.830
	After	64 ± 21	65 ± 14	-0.080	0.930

Data are shown mean ± Standard deviation. ARA = Action Research Arm

Table 4. Presentation of the mean values of the initial global functional and autonomy scores and the end of treatment according to sex

Parameters		Duration of disease		t	*p* value
		Male	Female		
% ARA	Before	51 ± 21	53 ± 22	-0.330	0.74
	After	66 ± 20	61 ± 22	0.66	0.51
% Fugl Meyer	Before	50 ± 21	52 ± 22	-0.240	0.81
	After	66 ± 15	62 ± 21	0.610	0.54

Data are shown mean ± Standard deviation. ARA = Action Research Arm

rehabilitation, whose average age was 59.6 ± 8.5 years, with extremes of 43 years and 79 years. Male predominance was observed. The same trend has been described in other Congolese series in relation to the average age and male predominance [1, 2]. But our average age turns out to be lower than that described in the foreign series [3-6]. This age disparity of patients can be explained on the one hand by the fact that the European population is more aging than ours, but also by the precariousness of the preventive measures in our environment making the subjects are exposed at an early age cardiovascular risk factors,

Table 5. Presentation of the mean values of the initial global functional and autonomy scores and the end of treatment according to age

Parameters		Age (years)		t	*p* value
		< 65	≥ 65		
% ARA	Before	60 ± 17	32 ± 15	4.150	0.001
	After	74 ± 15	42 ± 13	5.45	0.001
% Fugl Meyer	Before	59 ± 18	31 ± 14	4.012	0.042
	After	72 ± 15	49 ± 12	4.021	0.006

Data are shown mean ± Standard deviation. ARA = Action Research Arm

including stroke.

The majority of these patients had ischemic stroke (70%), and the left hemi-body was most interested in paralysis or paresis (60%). Most of them were beyond one year of their illness (53.3% of cases between 6 and 11 months of illness, and 46.7% at least 12 months).

In relation to the level of motor, functional and autonomy evolution of these patients before the program, it appears that it was practically average, ie an overall average score of ARA (motor level of the upper limb) to 51% and a motor level at the Fugl meyer scale overall at 50%. This level of motor and average autonomy found in these patients at the beginning of the program can be explained because they were already at least 6 months of their stroke, considered as phase of maintenance in community [7], which is not possible only when the range score is normally ≥ 60/100 [8]. In addition, Fugl Meyer's hand motility was the most disturbed (at 6/14), with a pinch score at the lower ARA (ie 3/18) than the others under scales. This tendency can be justified first of all by the fact of the important representation of the hand at the level of the brain (homunculus of penfil), and by its motricity which is more fine and discriminative than the other parts of the body.

By analyzing the impact of stress-induced therapy on the various motor, functional and autonomy parameters selected, we recorded a very significant difference in their overall mean values. Including an ARA score of 51 ± 21% at baseline and 64 ± 20% at the end of treatment, with a $p = 0.001$; on the other hand, the analysis of the subscores did not show any significant difference in pinching (initially 3/18 for 4/18 at the end) and overall movements (5/9 initially for 6/9 at the end), with a $p > 0.05$. The difference in mean values at the Fugl Meyer scale was also very significant, both at overall scores and under-scores ($p < 0.05$). Our results corroborate with those of Bofosa *et al*. [5] who compared the level of motor development among patients undergoing induced stress therapy (IDC) found a very significant improvement ($p = 0.001$) for the group of patients undergoing TCI at the end of the program.

The good motor evolution observed after induced stress has been demonstrated in the randomized Excite study by Wolf *et al*. [9], published in 2006, justified by its intensive character, it significantly improves the quality and speed of movement in the patients who practice it.

Moreover, it is currently reported that rehabilitation is giving more and more place to assets; Daviet [10] synthesized the main studies validating the principles of motor learning insisting on active patient participation, the need for repeated gestures, in an intense and task-oriented way. This trend is very much in TCI, and plays a key role in brain plasticity.

As for the comparison of the mean values of the overall ARA and Fugl Meyer scores made according to the duration of the disease, we found no significant difference between patients who were less than 12 months old and those who more or less 12 months ($p > 0.05$). This comparison also showed no significant difference between men and women ($p > 0.05$).

The same observation was made in the series of Tshianga [11], where the difference was not significant between men and women for both motor skills score ($p = 0.89$) and autonomy score ($p = 0.86$). This trend has been reported in almost all literature and reviews [12-17] that sex does not appear to have an influence on functional outcome.

On the other hand, we found a very significant difference between the mean values of the overall

scores of the motor and independence scales between elderly patients (over 65) and younger patients (under 65) ($p < 0.05$) .

Tshianga [11, 15] in his series also found a very significant influence of age on the level of gross motor skills ($p = 0.001$) and autonomy ($p = 0.002$), ie better for patients under 65 than those over 65. However, there is controversy in the literature about the impact of age on functional becoming. Feigenson *et al*. [18], in a prospective study of 248 patients, does not retain age as a predictor of fate. Granger *et al*. [19] reported that old age significantly reduces the level of final functional independence. These disparities may be related to sample size, past lifestyle and other related factors, as some authors have reported that although recent work finds a relationship between age and functional becoming, it is note that the weight of age in functional becoming is less than that of other predictors [18, 19].

Limitations

This study is limited to the use of a small sample of a metropolitan city of the Democratic Republic of Congo and in the absence of control or comparative group, which will probably reduce the possibility of generalization of the results. Therefore, a future study of a more representative sample of hemiplegic patients and adding the control or comparative groupis needed to potentially increase the generalizability in the country.

CONCLUSION

This study shows that induced stress therapy has positive effects in motor and functional recovery of the upper hemiplegic limb. Sex and duration of illness were not positively influenced. On the other hand, the influence of age has been found. These results concern only the cases included in the study.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2020;6(4):300-307 Original Article

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The evaluation of relation between vitamin B12 and body mass index

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ABSTRACT

Objectives: Obesity has become a pandemy all around the world, etiology of obesity consist multiple factors and it causes serious health problems. It is known that the low level of vitamin B12 has adverse effects on many systems, mainly cell DNA. In our study, it was planned to evaluate whether there is a relation between body mass index and serum vitamin B12 level.

Methods: We included 168 patients aged 18-67 years, who did not have a chronic disease and who applied to the outpatient clinic in our center. We divided the patients into 3 groups according to the body mass index (BMI): Group I: normal weight (BMI: 18.50-24.99 kg/m2); Group II: overweight (BMI: 25-29.9 kg/m^2) and Group III: obese (BMI: ≥ 30 kg/m^2). Vitamin B12 levels were evaluated between these groups.

Results: There was a statistically significant difference between the groups in terms of glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride. Vitamin D levels were not statistically significant between the groups. The mean serum vitamin B12 levels of the individuals were 299 ± 125 pmol/L, 298 ± 148 pmol/L and 313 ± 143 pmol/L in Group I, Group II and Group III, respectively. There was no statistically significant difference and correlation between BMI and serum vitamin B12 levels in the groups.

Conclusions: The etiology of obesity, a serious health problem in today's society, has proven to be multifactorial. No significant association was found between BMI and vitamin B12 levels at the end of the study. It was concluded that similar studies should be performed with a large case series.

Keywords: vitamin B12, cobalamin, obesity, body mass index

Obesity, which is one of the most important health problems of the developed and developing countries in the world today, is a chronic energy metabolism disorder which is caused by excess fat accumulation in the body and can cause physical and mental problems [1]. Obesity is a complex disease involving appetite regulation and energy metabolism, not a simple eating problem due to lack of autocontrol [2]. Psychological, hormonal, metabolic disorders and pharmacological factors play a role in the formation of obesity, as well as various environmental factors that trigger genetic predisposition and impaired energy balance [3].

The endocrine, cardiovascular, respiratory, gastrointestinal, genitourinary and musculoskeletal system and skin, as well as psychosocial state are affected obesity at varying rates. In addition, studies have shown that obesity leads to various diseases such as

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malignancy (breast, over and endometrium in women, colon and prostate in men), gout, stroke and depression [4]. Many methods of measurement are used in the evaluation of obesity. Among these, the body mass index (BMI), which is practical in clinical practice, was first described by Quetelet in 1835 and is now the most commonly used method [5].

Vitamin B12 acts as an important coenzyme and cofactor in the synthesis of deoxyribonucleic acid (DNA) and is necessary for the maintenance of normal hematopoiesis and for the continuity of the nervous system [6]. Clinical findings are rare in vitamin B12 deficiency; however, hematologic, neuropsychiatric and gastrointestinal signs and symptoms are most frequently seen [7]. The prevalence of vitamin B12 deficiency in the whole population is not fully understood but it is known that the incidence of vitamin B12 deficiency increases with age. It is frequently seen in about 10-15% over the age of 60 [8, 9].

Many studies have shown that the etiology of obesity, a public health problem on a global scale, is multifactorial. It is known that the low level of vitamin B12 has adverse effects on many systems, mainly cell DNA. In our study, it was planned to evaluate whether there is a relation between body mass index and serum vitamin B12 level.

METHODS

We included 168 patients aged 18-67 years, who did not have a chronic disease and who applied to the outpatient clinic in our center from January 2015 to December 2016. Exclusion criterias were rheumatoid arthritis, ankylosing spondylitis, collagen tissue disease, celiac, hypo-hyperthyroidism, hematologic disease, malignancy, leukemia, lymphoma, malnutrition, malabsorption, and active infection. We also excluded patients previously treated with vitamin B12 and immunsuppressive drug. Written consent of the study participants, and ethics committee approval from our center were obtained. We divided the patients into 3 groups according to the BMI: Group I: normal weight (BMI: 18,50-24,99 kg/m^2); Group II: overweight (BMI: 25-29.9 kg/m^2) and Group III: obese (BMI: ≥30 kgm^2).

Complete blood counts were obtained with tubes containing ethylenediaminetetraacetic acid (EDTA) and examined with the Bt pro 2401 instrument. Biochemical measurements were determined by using a biochemical analyzer for serum glucose and lipid panel Cobas 6000 C501 (Roche Diagnostics GmbH, Mannheim, Germany) in blood samples taken after at least 12-14 hours of fasting. Serum vitamin D and vitamin B12 levels were determined by the Cobas e 411 (Roche Diagnostics GmbH, Mannheim, Germany) analyzer. The normal range of serum vitamin B12 was accepted as 200-800 pg/mL.

The height and weight of the subjects were measured to calculate BMI. Weight of the subjects was measured in the upright position after 12-14 hours of fasting. Height measurement of the subjects was made by measuring the distance from the head to the base, ensuring that the subjects were standing upright, with their feet naked and adjacent.BMI was calculated based as weight in kilograms divided by the square of the height in metres (kg/m^2).

Statistical Analysis

Statistical analyzes were performed using the SPSS 24.0 program (SPSS Inc. Chicago, IL). The normal distribution of the variables was tested by Kolmogorov smirnov and the variance equation by the Levene test. All analyzes were performed by parametric tests, since the data were normally distributed. Continuous variables were expressed as mean ± standard deviation, and categorical variables as percent.Independent-Samples T-Test for numerical variables and Chi square test for categorical variables were used to compare group averages. The relationship between BMI and biochemical parameters was assessed by Pearson correlation analysis. Parameters that were statistically significant in binary comparisons were included in the multivariate model. The results were evaluated in a confidence interval of 95% and a significance level of $p < 0.05$.

RESULTS

Of the 168 individuals included in the study, 125 (66.1%) were females and 43 (33.9%) were males. The average age is 37.6 ± 8.8 years. In all the subjects studied, the mean height was 166.0 ± 8 cm and the mean BMI was 27 ± 6.5 kg/m2. The patients were divided into 3 groups according to the BMI and 77

Table 1. Comparison of age, height, weight and BMI of groups

Variables	Group I (n = 77)	Group II (n = 35)	Group III (n = 56)	*p* value
Age (year)	27 ± 10	40 ± 12	46 ± 11	**< 0,001**
Height (cm)	164 ± 7	168 ± 8	164 ± 8	**0.034**
Weight (kg)	57 ± 8	78 ± 8	94 ± 17	**< 0.001**
BMI (kg/m²)	21 ± 2	28 ± 2	35 ± 5	**< 0.001**

patients, 35 patients and 56 patients were included in to the Group I (normal weight), Group II (overweight) and Group III (obese), respectively. When the cases grouped according to BMI were examined according to age; the mean age of the individuals in Group I was 27 ± 10 years, the mean age of individuals in Group II was 40 ± 12 years and the mean age of individuals in Group III was 46 ± 11 years. There was a statistically significant difference in age between groups ($p < 0.001$) (Table 1).

When the groups were examined according to the serum glucose levels, the mean serum glucose level of the individuals was 90 ± 8 mg/dL, 96 ± 10 mg/dL, and 103 ± 14 mg/dL in Group I, Group II and Group III, respectively. There was a statistically significant difference between the groups in terms of serum glucose level ($p < 0.001$) (Table 2).

When the groups were examined according to the mean serum total cholesterol level, mean total cholesterol levels were 162 ± 32 mg/dL in Group I, 193 ± 45 mg/dL in Group II and 195 ± 43 mg/dL in Group III. Mean serum LDL-cholesterol levels; 93 ± 24 mg/dL in Group I, 120 ± 36 mg/dL in Group II and 122 ± 37 mg/dL in Group III. When the groups were examined according to the mean HDL-Cholesterol level, mean HDL cholesterol levels were detected 54 ± 12 mg/dL in group I, 48 ± 13 mg/dL in group II and 46 ± 12 mg/dL in group III. Mean serum triglyceride levels were 81 ± 30 mg/dL in Group I, 135 ± 97 mg/dL in Group II and 138 ± 68 mg/dL in Group III.There was a statistically significant difference between the groups in terms of total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride ($p < 0.001$) (Table 2).

When the serum vitamin D levels of the groups were examined, the mean serum vitamin D level of the individuals was 12 ± 11 ng/mL, 13 ± 5 ng/mL and 13 ± 7 ng/mL in Group I, Group II and Group III,

Table 2. Comparison of glucose and lipid levels of groups

Parameters	GROUP I (n = 77)	GROUP II (n = 35)	GROUP III (n = 56)	*p* value
Glucose (mg/dL)	90 ± 8	96 ± 10	103 ± 14	**< 0.001**
Total Cholesterol (mg/dL)	162 ± 32	193 ± 45	195 ± 43	**< 0.001**
LDL-Cholesterol (mg/dL)	93 ± 24	120 ± 36	122 ± 37	**< 0.001**
HDL-Cholesterol (mg/dL)	54 ± 12	48 ± 13	46 ± 12	**< 0.001**
Triglyceride (mg/dL)	81 ± 30	135 ± 97	138 ± 68	**< 0.001**

Table 3. Comparison of serum vitamin D levels in groups

Variables	Group I (n = 77)	Group II (n = 35)	Group III (n = 56)	*p* value
BMI (kg/m²)	21 ± 2	28 ± 2	35 ± 5	0.750
Vitamin D (ng/mL)	12 ± 11	13 ± 5	13 ± 7	

Table 4. Comparison of serum vitamin B12 levels in groups

Variables	Group I (n = 77)	Group II (n = 35)	Group III (n = 56)	*p* values	r values
BMI (kg/m²)	21 ± 2	28 ± 2	35 ± 5	0.430	0.014
Vitamin B12 (pmol/L)	299 ± 125	298 ± 148	313 ± 143		

respectively. There was no statistically significant difference in serum vitamin D levels between the groups ($p = 0.750$) (Table 3).

The mean serum vitamin B12 levels of the individuals in Group I were 299 ± 125 pmol/L, the mean serum vitamin B12 levels of the individuals in Group II were 298 ± 148 pmol/L and the mean serum vitamin B12 levels of the individuals in Group III were 313 ± 143 pmol/L. There was no statistically significant difference and correlation between BMI and serum vitamin B12 levels in the groups ($p = 0.430$, R = 0.014) (Table 4) (Fig. 1).

DISCUSSION

Obesity is a multifactorial and complex disease that is the result of interaction of genetic and environmental factors [10]. The main risk factors for obesity development are; decreased physical activity, wrong eating habits, increasing age, being female, number of births, marriage, smoking and alcohol intake. Reasons for the progressive increase in obesity, a decrease in activity due to sedanter's lifestyle and an increase in fast food-style eating habits and excessive calorie intake [3].

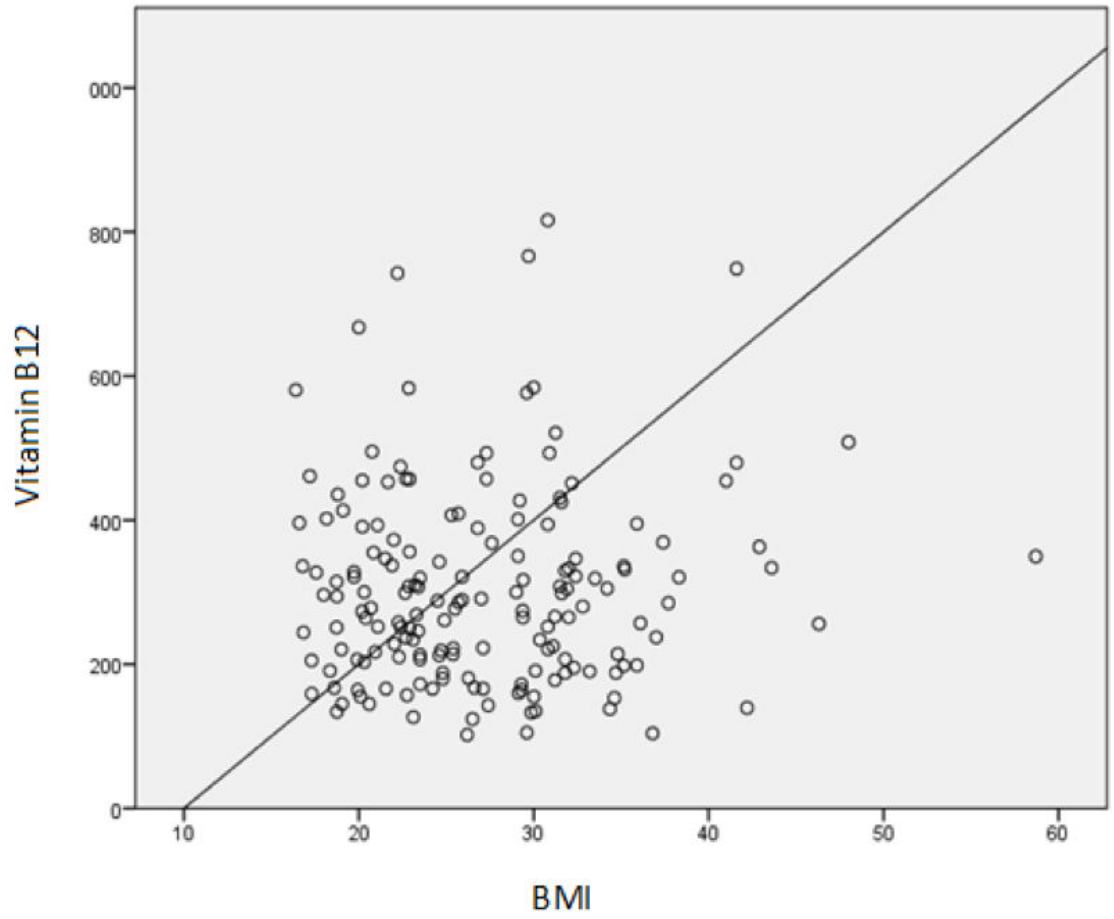

Fig. 1. Correlation of BMI and serum vitamin B12 levels.

In some studies evaluating the relation of obesity with age, an increase in obesity was observed with increasing age [11]. In a study conducted by Lagunova *et al*. [12], in which 2126 subjects were included, a significant relationship was found between BMI and age. In another study conducted by Akman *et al*. [13], it was observed that the prevalence of obesity increased in parallel with the increase in age up to the age of 60. Similar to these studies, there was a statistically significant difference between the groups in terms of the age groups grouped according to BMI ($p < 0.001$).

Many studies have shown that abdominal fat tissue accumulation, an indicator of obesity, is associated with atherogenic and diabetic disorders such as insulin resistance, hyperinsulinemia, glucose intolerance, dyslipoproteinemia, and hypertension. The relative risk of diabetes mellitus increases up to 60.9% when BMI exceeds 35 kg/m^2 [14]. It is thought that the duration of obesity and its type, that is, central type fat accumulation, is more effective in the development of diabetes mellitus and glucose intolerance than the degree of obesity [15, 16]. A study conducted by Kutlutürk *et al*. [17] investigated the relationship between obesity and metabolic risk factors and found a significant relationship between obesity and fasting serum glucose levels. Innocent *et al*. [18] found a positive but weak correlation between BMI and serum glucose level in their studies. Similar to these studies, in our study, there was a statistically significant difference in serum glucose levels between the subjects grouped according to BMI ($p < 0.001$).

Obesity causes adverse changes in lipid metabolism. These include high total cholesterol, LDL-cholesterol, VLDL-cholesterol, triglyceride levels and low HDL-cholesterol.HDL-cholesterol levels were 5% lower in obese subjects [19]. In general, in obese subjects, fasting plasma triglyceride values tend to increase and plasma HDL-cholesterol levels tend to decrease [20]. In a study conducted by Faheem *et al*. [21], a total of 2,270 patients were included in the study, and a positive correlation was found between the BMI and cholesterol parameters. In our study, when the cases were grouped according to BMI, there was a negative correlation between BMI and total cholesterol, LDL-cholesterol and triglyceride, and a negative correlation between BMI and HDL-cholesterol.

Low vitamin D levels have been demonstrated in many studies involving obesity, diabetes mellitus, and the metabolic syndrome. This relationship is explained by the demonstration of vitamin D receptor) (VDR) expression in fat tissue, the solubility of vitamin D in fat and its storage in fat tissue. However, vitamin D has been shown to play a role in the modulation of insulin production and secretion in animal studies, with a negative correlation between BMI and vitamin D levels. Active vitamin D has been shown to stimulate calcium exchange in pancreatic β cells and mouse models in vitro. There is strong evidence that vitamin D affects the release of insulin from β-cells of the pancreas, and that active vitamin D inhibits lipolysis and exhances lipogenesis by inhibiting uncoupling protein-2 protein in fat cells. In mice without VDR, it was reported that all fat mass decreased, serum leptin level decreased and energy consumption increased [22, 23].

There are, however, studies suggesting that there is no significant relationship between vitamin D levels and obesity. In Gronborg *et al*.'s study [24], it was observed that there was basically no relation between vitamin D level and body fat ratio, and body fat ratio did not respond to vitamin D supplementation. In our study, there was no statistically significant difference in serum vitamin D levels between the cases grouped according to BMI ($p = 0.750$). All of the groups in our study had vitamin D deficiency.It is thought that vitamin D deficiency in all groups is due to the fact that the geographical region where we are studying is high altitude, heavy winter climate, low sun light due to climate conditions and low exposure sunlight due to clothing style.

Vitamin B12, which plays a vital role in the functioning of many important molecules and hormones, especially in the production of DNA, which is essential for cell division and proliferation, is an important essential vitamin. It can not be synthesized in the human body and is abundant in proteins, especially those derived from animal origin. Approximately 6 micrograms per day should be taken [7]. It can be stored in small quantities in the body, 80% of which occurs in the liver. In the case of deficiency, it takes 3-4 years for clinical signs to appear in case of deficiency [25].

The prevalence of vitamin B12 deficiency in the world is not known precisely. However, it is generally

known that the incidence increases with age. In one study, vitamin B12 deficiency was detected in about 15% of people over 65 years of age.In general, the incidence of vitamin B12 deficiency in adults is 5-20% on average [8, 26, 27]. In a surveillance study in the United States; when the basal level of vitamin B12 was taken as 148 pmol/L, vitamin B12 deficiency was found in 3% between 20-39 years, 4% between 40-59 years and 6% over 60 years. In another study, vitamin B12 deficiency was found to be 14-16% between 20-59 years and 20% over 60 years when taking 221 pmol/L [28, 29].

Vitamin B12 is a cofactor in methionine synthesis from homocysteine [30]. Deficiency of vitamin B12 causes hyperhomocystinemia. Cohort studies have shown that even mild hyperhomocystinemia increases cardiovascular morbidity and mortality [31, 32]. Martos *et al*. [33] found that hyperhomocystinemine correlates with insulin resistance in obese prepubertal children [33]. Güven *et al*. [34] found low levels of vitamin B12 in patients with adult metabolic syndrome compared to normal healthy individuals. In another study, it was shown that homocysteine levels returned to normal range with folate and vitamin B12 treatment in patients with metabolic syndrome with low serum folate and serum vitamin B12 levels. It has been found that it has a positive effect on the recovery of insulin resistance and contributes to the regression of endothelial dysfunction [35].

In the study performed by Baltaci *et al*. [36], 680 female subjects aged 18-68 years were divided into two groups as obese and normal weight according to BMI and serum vitamin B12 level was found to be low in the group with high BMI. In this study, it was suggested that in obese individuals, vitamin B12 deficiency is independent of nutritional status. In the same study, there was no correlation between serum vitamin B12 levels and insulin resistance and visceral obesity [36]. In a study conducted by Ho *et al*. [37], a significant portion of obese adolescents bearing the risk of type 2 diabetes mellitus were found to have low or borderline serum vitamin B12. In addition, negative correlations were found between serum vitamin B12 levels and BMI in this study [37]. In a study conducted by Goyal *et al*. [38] , authors reported that serum vitamin B12 deficiency was more common in the morbidly obese population. In another study, 995 women who were on the 28th week of their gestation were included to the study and a 0.6% decrease in serum vitamin B12 was detected for every 1% increase in BMI. However, the differences in socioeconomic status, the presence of vitamin supplements or vegetarian diet-style nutrition, the number of parities and the lack of full exclusion of hemodilution due to pregnancy were the the limitation of the study [39].

In a study, 228 normal weight and 164 obese participants included to the study and serum vitamin B12 levels were found to be low in 10.4% of the obese participants and only 2.2% of the participants with normal weight [40]. The authors explained that the reason for this that the nutritional content of obese individuals is low in terms of vitamin B12 despite being rich in terms of carbohydrate and fat [40]. In another study, serum vitamin B12 levels were examined in adolescents between 10 and 17 years of age with clinical features of pre-diabetes and/or insulin resistance [41]. In adolescents with serum vitamin B12 level ≤ 221 pmol/L, BMI was higher and gender difference was not observed. It was emphasized that this low level was caused by low vitamin B12 in the nutritional content [41]. Vitamin B12 plays an important role in DNA methylation. Recent genomic analysis has suggested that increased DNA methylation is associated with increased BMI in adults [42].

On the other hand, in a study involving Brazilian overweight adolescents, serum vitamin B12 concentrations were compared with BMI and no significant difference was found [43]. In the study conducted by Reitman *et al*. [44], there was no statistically significant difference in the levels of serum vitamin B12 in patients overweight and obese compared to those in normal weight. Abu-Samak *et al*. [45] found that the mean serum vitamin B12 level was low in overweight (BMI = 25-29.9 kg/m^2), but there was no decrease in vitamin B12 levels in obese (BMI ≥ 30 kg/m^2). El-Quadah *et al*. [46] observed that serum vitamin B12 levels increased as the BMI increased for the subjects included in the study.

In our study, when the serum vitamin B12 levels of the cases grouped according to BMI were examined, serum vitamin B12 levels of the individuals in Group I were 299 ± 125 pmol/L, serum vitamin B12 levels of the individuals in Group II were 298 ± 148 pmol/L serum vitamin B12 levels of the individuals

were 313 ± 143 pmol/L.There was no statistically significant difference in serum vitamin B12 levels between the groups. Statistical analysis of serum vitamin B12 and BMI did not reveal significant association (p = 0.430, R = 0.014).

CONCLUSION

As a result, the etiology of obesity, a serious health problem in today's society, has proven to be multifactorial. In this study, we also investigated whether there is a relationship between vitamin B12 and obesity. However, the retrospective nature of our study and the inclusion of only a small cross-sectional group were among the limitations of this study. No significant association was found between VKI and vitamin B12 levels at the end of the study. It was concluded that similar studies should be performed with a large case series.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Agricultural injuries encountered in Giresun, which is an agricultural city of Turkey

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ABSTRACT

Objectives: This study aimed to determine the demographic and clinical features of gardening injuries in an agricultural city and to provide some suggestions to reduce the incidence of agricultural injuries.

Methods: This study assessed 419 gardening injuries that were admitted to the emergency department of Giresun University Prof. Dr. Ilhan Özdemir Training and Research Hospital between June 30, 2015 and November 1, 2015. We retrospectively examined all the documents, x-rays, tomographies, and tomography reports related to the cases.

Results: Falls from a height (19.3%), falls (31.5%), foreign body crashes (FBCs) (14.8%), sharp-penetrating object injuries (SPOIs) (29.8%), and motorized/motorless device injuries (MMDIs) (4.5%) were the major categories of gardening injuries. Most of the falls from a height were from a tree (86%), primarily fig trees (54.3%). SPOIs primarily affected the hand-wrist area with 82 cases (65.6%); the most common sharp tools that caused injury were sickle-scythes (47.2%) and axes (35.2%). FBCs frequently affected the eyes (48.4%) and head region (17.7%), and tree branches were the most common foreign bodies causing such crashes (38.7%). MMDIs were caused primarily by haymaker harvester machines (42%). Three cases died (0.7%), and 305 cases (72.8%) were discharged after emergency treatment. Additionally, 115 cases (27.5%) were hospitalized, 11 cases underwent urgent surgery, and 63 cases underwent elective surgery. Using uncuttable gloves, socks, and knee-guards could prevent 88% of SPOIs. Furthermore, eyewear and head guards could prevent 60.1% of FBC injuries.The usage of fall arrest equipment particularly for only fig and pear tree types could prevent 68.6% of the falls from a tree.

Conclusions: Gardening injuries are significant traumas in agricultural regions. By implementing simple and cheap security measures, we can prevent destrucitive traumas.

Keywords: injury, agricultural injury, gardening injury, farm injury, back yard injury, trauma, work-related injury

Giresun is a city on the northeastern part of Turkey that is famous for its nature and greens and blues. Giresun is located on the shore of the Black Sea. Turkey is a pioneer in hazelnut production worldwide, and Giresun ranks first in this production with its high-quality hazelnuts.

Turkey is the leader of world nut export with 65.5%. Giresun is on the first rank of nut export

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among the cities of Turkey.Almost all the locals in Giresun have their own nut, fruit, and vegetable gardens. In addition to nuts, they commonly grow fruits, including cherries, apples, pears, figs, grapes, plums, and cherry laurel, and vegetables, including black cabbage, corn, potatoes, green beans, parsley, fresh mint, and lettuce.

gardens are mostly grown on inclined terrain, which can easily cause injuries such as falls. Stones, wood, soil, and weeds can slip down and hit a human. Furthermore, the gardeners use sharp objects during gardening, which can cause injuries.

Hazelnut trees are short, and the nuts are picked by pulling the branches down or by picking the nuts up from the ground. During this activity, the branches can hit the head, particularly the eyes, and dust can transfer foreign bodies to the eyes. Moreover, some people use motorized or motorless devices to carry the crops, separate the nut and its green shell, etc., and these devices can cause injuries.

Our hospital has experienced many cases of gardening injuries. Therefore, we aimed to identify the most common types of gardening injuries and suggest some solutions to reduce the damage.

METHODS

This study assessed gardening injury cases that were admitted to the emergency department of the Giresun University Prof. Dr. Ilhan Özdemir Training and Research Hospital between June 30, 2015 and November 1, 2015. We retrospectively examined all the documents, x-rays, tomographies, and tomography reports. Traffic accidents on the way to the garden, allergic reactions, insect bites, and animal-related injuries were not included in this study.

Statistical Analysis

The IBM SPSS 17.0 (IBM Corporation, Armonk, NY, USA) program was used to analyze the data.

RESULTS

The mean age of the study population was 49.4 ± 18.0 years (range 3-97). Additionally, 66.6% (n = 279) of cases were male and 33.4% (n = 140) were female. The patients were most frequently admitted to the hospital in August (38.2%), September (23.6%), July (22.4%), and October (14.8%).

The most common types of injuries were falls (31.5%, n = 132), sharp-penetrating object injuries (SPOIs) (29.8%, n = 125), falls from a height (19.3%, n = 81 cases), foreign body crashes (FBCs) (14.8%, n = 62), and motorized/motorless device injuries (MMDIs) (4.5%, n = 19), as shown in Fig. 1.

The SPOIs were caused primarily by sickle-scythes (47.2%, n = 59), axes (35.2%, n = 44), saw machines (12%, n = 15), string trimmers (4.8%, n = 6), and curved knifes (0.8%, n = 1). The body parts most commonly affected by SPOIs were hands-wrists (65.6%, n = 82), foot-ankle (11.2%, n = 14), and knees (11.2%, n = 14), as shown in Table 1.

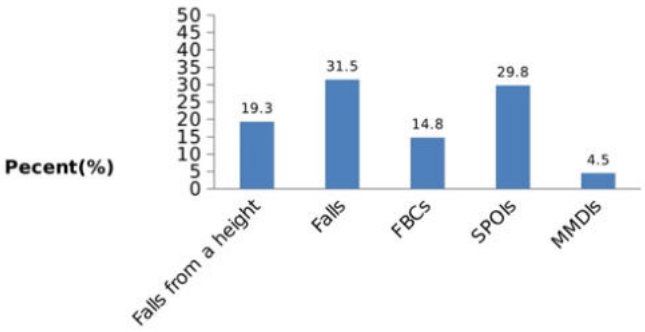

Fig. 1. Types of injuries. FBCs = Foreign body crashes, SPOIs = Sharp-penetrating object injuries, MMDIs = Motorized/Motorless device injuries.

Table 1. Regions of sharp-penetrating object injuries (SPOIs)

Region	Number of cases	Percent
Hand-wrist	82	65.6
Knee	14	11.2
Foot-ankle	14	11.2
Arm	4	3.2
Shin	3	2.4
Forearm	2	1.6
Thigh	2	1.6
Head	2	1.6
Elbow	1	0.8
Ear	1	0.8
Total	125	100

There were three primary types of falls from a height: from a tree (87%, n = 70), from a steep slope (12%, n = 10), and from long ladders (1%, n = 1). As shown in Table 2, the falls were mostly from fig trees (54.3%, n = 38), pear trees (14.3%, n = 10), walnut trees (5.7%, n = 4), and cherry laurel trees (5.7%, n = 4).

FBCs were caused by tree branches (38.7%, n = 24), stones (19.4%, n = 12), soil-weeds-dust (19.4%, n = 12), and wood-trunks (17.7%, n = 11), as shown in Table 3.

As shown in Table 4, the body parts most commonly affected by FBCs were the eyes (48.4%, n = 30), head (17.7%, n = 11), and foot-ankle (11.3%, n = 7).

Most instances of MMDIs occurred from using chugs (42%, n = 8), followed by haymaker harvester machines (21%, n = 4), telphers (21%, n = 4), hazelnut ventilators (11%, n = 2), and quad bikes (5%, n = 1), as shown in Fig. 2.

The primary clinical findings were only soft tissue damage (37.7%, n = 158), simple cuts (28.9%, n = 121), extremity fractures (14.1%, n = 59), tendon cuts (9.3%, n = 39), and vertebra fractures (8.6%, n = 36). Table 5 shows the other clinical findings.

The vertebral fractures were primarily located in the lumbar (47.2%, n = 17), thoracic (36.1%, n = 13), and cervical (5.6%, n = 2) spine. Two cases (5.6%) had both cervical-thoracic fractures, and two cases (5.6%) had both thoracic-lumbar fractures.

In total, 305 (72.8%) patients were discharged after receiving treatment in the emergency department. Additionally, 105 (25.1%) patients were hospitalized and 10 (2.4%) patients were transferred to another hospital. Three patients (0.7%) died in our hospital.

The neurosurgery department treated 28.6% (30 cases) of the hospitalized patients whereas the plastic reconstructive surgery, orthopedics, and thoracic surgery departments treated 22.9% (n = 24), 21.9% (n = 23), and 13.3% (n = 14) of the patients, respectively. Additionally, 10.5% (n = 11) of patients were admitted to the general surgery department and 1.9% (n = 2) were admitted to pediatric surgery. Only one patient (0.9%) who had been admitted to the ophthalmology department was hospitalized.

An urgent operation was performed in eleven cases, six (55.5%) of which were performed by plastic-reconstructive surgeons and five (45.5%) of

Table 2. Type of the tree

Type of the tree	Number of cases	Percent
Fig	38	54.3
Pear	10	14.3
Walnut	4	5.7
Cherry laurel	4	5.7
Plun	3	4.3
Hazelnut	3	4.3
Apple	2	2.9
Linden	2	2.9
Cherry	2	2.9
Grape	2	2.9
Total	**70**	**100**

Table 3. Reasons of foreign body crashes (FBCs)

Foreign body crash (FBC)	Number of cases	Percent
Tree branch	24	38.7
Stone	12	19.4
Soil-weed-dust	12	19.4
Wood-trunk	11	17.7
Nail	2	3.2
Water resorvoir cover	1	1.6
Total	**62**	**100**

Table 4. Regions of foreign body crashes (FBCs)

Region	Number of cases	Percent
Eye	30	48.4
Head	11	17.7
Foot-ankle	7	11.3
Shin	3	4.8
Ear	3	4.8
Hand-wrist	2	3.2
Thigh	2	3.2
Chest-back	2	3.2
Forearm	1	1.6
Thigh + Chest-back	1	1.6
Total	**62**	**100**

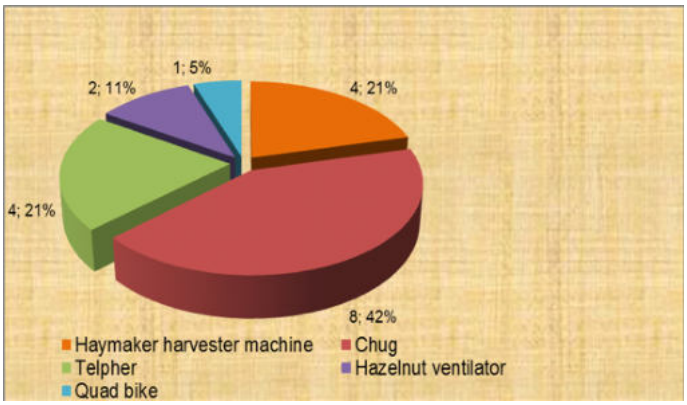

Fig. 2. **Types of motorized/motorless device injuries.**

Table 5. **Clinical Findings**

Clinical finding	Number of cases	Percent
Only soft tissue damage	158	37.7
Simple cut	121	28.9
Extremity fractures	59	14.1
Tendon cut	39	9.3
Vertebra fractures	36	8.6
Intrathoracal injury	23	5.5
Amputation/circulatory impairment	10	2.4
Intraabdominal injury	7	1.7
Intracranial injury	5	1.2
Wide tissue defect or need of flap	5	1.2
Shoulder dislocation	3	0.7
Total	**419**	**100**

which were performed by neurosurgeons. Sixty-three patients underwent elective operations in the following departments: plastic reconstructive surgery (47.6%, n = 30), orthopedics (34.9%, n = 22), neurosurgery (14.3%, n = 9), general surgery (1.6%, n = 1), and ophthalmology (1.6%, n = 1).

DISCUSSION

Agricultural injuries are increasing daily [1] and have a high risk of mortality and morbidity. Agricultural populations, governments, and municipal authorities should pay attention to gardening injuries and tighten safety measures.

The mean age of the injured population in this study was younger [2] or similar [3, 4] to that reported in previous studies. In Giresun, people tend to work in their own gardens with few seasonal workers. Our study included both a three-year-old child who was picking up hazelnuts from the ground and a 97-year-old woman who was helping her children in a hazelnut garden.

Das [2] reported 323 cases of farming injuries in West Bengal in India. Most of the patients were injured by hand tools (64.7%), followed by injuries from farm machinery (29.1%) and others (6.2%) including dermatologic and respiratory problems, etc. [2]. Browning *et al*. [5] reported on the incidence of injuries from falls (24.9%), machinery (22.5%), wood-cutting (14.6%), and animal-related events (14.3%) in Kentucky among the farmers who were older than 55. Zhou and Roseman [6] reported that the external causes of farm operator injuries in Alabama were machinery (28.6%), falls (23.2), and animal-related (12.5%). Twari *et al*. [7] reported on the agricultural injuries of Central India. They highlighted the incidence of injuries from farm machinery (77.6%), hand tools (11.8%), and others (10.6%), including snakebites, wells, etc. Another study revealed that 30.1% of injuries were fall-related, 39.8% were machine-related, and 16.1% were animal-related [4]. In our study, many of the patients were injured in their own gardens; few seasonal workers were included. We did not include dermatologic, respiratory, or animal-related injuries in our study. Some motorized or motorless vehicles caused injuries in our study; however, Giresun has rugged terrains, so falls were the primary cause of injury. Sharp objects or hand tools are also used frequently in Giresun. FBCs are relatively commonly because of the rugged terrain and hazelnut tree branches.

One previous study reported on 222 sharp and penetrating object injuries that were primary caused by daos (n = 144, 60%), spades (n = 19, 8%), sickles (n = 18, 7%), and axes (n = 8, 3%); feet and legs were the most frequently injured body parts [8]. Another study reported on injuries with hand tools that were caused primarily by spades, sickles, cutters, etc. [2]. Zhou and Roseman [6] reported that the limbs were the most frequently injured body part. Twari *et al*. [7]

reported that 11.8% of injuries were caused by hand tools, primarily sickles and pickaxes. We found that 71.2% of injuries were upper extremity injuries and 26.5% were lower extremity injuries. The dao and spade were not used as tools in our region. Additionally, 65.6% of injuries were hand-wrist injuries and 11.2% were foot-ankle injuries. If the authorities support the use of only uncuttable clothe for distal parts of the extremities, we could eliminate 76.8% of SPOIs. Additionally, the usage of uncuttable knee-guards will help prevent 88% of SPOIs.

Falls from a height are very dangerous and can result in death. Falls from trees are the major cause of this type of injury. Some tree types are more hazardous than others; these tree types can be determined locally, and measures can be taken to prevent falls from these trees. Previous studies showed that coconut [9], walnut [10], and other trees were the most hazardous types in those study regions. In our region, patients most frequently fell from fig (54.3%) and pear trees (14.3%). If the authorities support the use of fall arrest equipment particularly for these tree types, 68.6% of the falls will be preventable for Giresun citizens.

FBCs are an important type of agricultural injury. In previous studies, falling branches, falling fruits, machine-related injuries, etc. are mentioned as factors for injury [11-14]. In our region, patients were often struck by hazelnut tree branches in the eyes and experienced soil-weed-dust related injuries of the eyes. Some of these cases resulted in ocular rupture. The population's awareness of eye health is very poor. Authorities should advise the use of eye protectors, eye glasses, or goggles, particularly for harvesting hazelnuts. In turn, 48.4% of these injuries can be prevented. Many studies advise the use of eyewear such as goggles to prevent work-related injuries to the eye [14-16]. Additionally, the use of head guards can prevent 60.1% of FBC injuries.

Simple cuts and soft tissue damage were the most common injuries, similar to previous studies [2, 7]. Farm machinery and motorized/motorless devices such as tractors, threshers, animal-drawn puddlers, winnowers, electric pump sets, power tillers, and speed sprayers were not frequently used in Giresun; however, other studies reported on injuries caused by these devices [2, 7, 17, 18]. Chugs, telphers, and haymaker harvester machines are more commonly used in Giresun.

Allen *et al*. [3] published an original article on 2294 farm-related injuries in North Carolina. In total, 82.1% of the patients were discharged from the emergency department, 12.1% were admitted to the hospital, 3.8% were transferred to another hospital, and 0.4% died [3]. In one study, the hospitalization rate was 43.9% and the mortality rate was 1.6% [4]. Our study included three patients who died from a gardening injury. We do not know the outcomes of the patients who were transferred to other hospitals; thus, the mortality may be higher. One of our patients died from a simple fall. She experienced a traumatic subarachnoidal hemorrhage. Another patient died as a result of a quad bike crash. The last patient had three toes amputated on his foot after a piece of wood crushed it; he died as a result of complications of the operation.

Limitations

This study was a retrospective study and a considerable amount of cases may be overlooked. Study duration was restricted to 5 months. The cases that transferred to the other hospitals could not be followed so we don't know the real mortality and morbidity. Insect bites, traffic accidents of workers, animal-related injuries, allergic diseases were not included in this study.

CONCLUSION

Gardening injuries are important traumas for agricultural regions.If we tighten security measures simply and cheaply we can prevent destructive traumas.

Conflict of interest

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The European Research Journal 2020;6(4):314-318 Original Article

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Graves' disease and thyroiditis can be differentiated using only free thyroid hormone levels

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ABSTRACT

Objectives: As the treatment approaches of Graves' disease and thyroiditis are different, differential diagnosis is important. In this study, we analyzed whether it is possible to perform a differential diagnosis for these two conditions by checking the increase ratio of free thyroid hormones.

Methods: In total 156 patients were taken into this study of which 29 were thyroiditis (17 had subacute thyroiditis, 6 had post-partum and 6 had silent thyroiditis) and 127 were Graves patients. The age, free T3 (FT3), free T4 (FT4), thyroid stimulating hormone (TSH) levels, FT3 index (FT3/FT3 upper limit of normal (ULN)), FT4 index (FT4/FT4 ULN) and free thyroid hormone index (FTHI) (FT3 index/FT4 index) of all patients were determined.

Results: A significant difference was found between the mean TSH, FT3 and FT3 index between Graves' disease and thyroiditis ($p = 0.036$, $p = 0.001$ and $p = 0.001$, respectively). When the groups were compared in terms of FTHI, the difference was found statistically significant ($p = 0.001$). FTHI was above 1 in all patients with Graves' disease whereas it was found below 1 in all patients with thyroiditis. There were no statistically significant difference between the Graves' disease and the thyroiditis in terms of age, FT4 and FT4 index ($p = 0.748$, $p = 0.389$ and $p = 0.392$, respectively).

Conclusion: Based on these results, considering the increases in free thyroid hormone values we can say that it is possible to perform a differential diagnosis of Graves' disease and thyroiditis, and that this may be used as a practical method to differentiate these two conditions.

Keywords: Graves' disease, thyroiditis, free thyroid hormone index

Thyrotoxicosis is a hypermetabolic condition characterized with excess serum thyroid hormones. It may occur as a result of exogenous thyroid hormone intake, release of previously synthesized hormone orhyperthyroidism. Hyperthyroidism is characterized by the high serum thyroid hormone levels as a result of excess synthesis and secretion of thyroid hormones from the thyroid gland. The most common causes are Graves'disease, toxic nodular goiter and toxic multinodular goiter [1, 2]. Graves'disease is an organ specific autoimmune disease. In Graves'disease the autoimmunity is against the thyroid stimulating hormone (TSH) receptor and the resultant TSH receptor antibodies cause hyperthyroidism [3, 4]. Graves'disease leads to diffuse extension in thyroid gland, ophtalmopathy in the eye, dermatopathy on the skin and acropachy in joints. In general, hyperthyroidism is treated through anti-thyroid drugs [5].

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Thyroiditis is also a common cause of thyrotoxicosis. Subacute thyroiditis is a condition that causes thyrotoxicosis as a result of stored thyroid hormone penetrating to blood after the inflammation of thyroid gland following upper respiratory tract infection. It is characterized with swelling in the neck region, pain and fever [1]. Post-partum thyroiditis is the inflammation of the thyroid gland after delivery. It causes painlessgoiter and temporary thyrotoxicosis. It is frequently observed between postpartum 6th week and 6th month, and generally, there is a family history for autoimmune diseases [1]. In the majority of the painless or silent thyroiditis patients, it is identified as an autoimmune disease characterized with antithyroid peroxidase (anti-TPO) positivity. Its pathological findings are characterized by lymphocyte infiltration in thyroid tissue. It is most frequent during postpartum period. Postpartum thyroiditis is accepted as a variant of silent thyroiditis. Silent thyroiditis may also occur in non-pregnant women and men. They show triphasic pattern; the differential diagnosis from GD should be performed at hyperthyroid phase and from Hashimoto thyroiditis at hypothyroid phase. While beta-blockers are used in all forms of thyrotoxicosis, as thyrotoxicosis in thyroiditis develops after destructive process, the anti-thyroid drugs have no effect and they are contraindicated [2, 6, 7]. For the proper treatment of thyrotoxicosis, accurate diagnosis is important.

In this study, we analyzed the increase ratio of free T3 (FT3) and free T4 (FT4) compared to their upper limit of normal (ULN) and the free thyroid hormone indices (FTHI) (FT3 index/F4 index) and examined whether these parameters may be used in the differential diagnosis of Graves'disease and thyroiditis.

METHODS

In total 156 patients were taken into this study of which 127 patients (69 female, 54.3%) were Graves'disease (6 patients under 18 years of age) and 29 cases (18 female, 62%) were thyroiditis (17 subacute thyroiditis, 6 post-partum and 6 silent thyroiditis, 3 patients under 18 years of age) who were all diagnosed through differential diagnosis. For this study, the permission was obtained from the ethical committee of our university. Patients with TSH value below 0.1 were accepted to the study.

The age, FT3 (normal reference range: 2-4.4 ug/ml), FT4 (normal reference range: 0.8-1.7 ng/dl), TSH (normal reference range: 0.27-4.2 U/ml), FT3 index (FT3/FT3 ULN), FT4 index (FT4/FT4 ULN) and FTHI criteria of the patients included to the study were controlled. FT3, FT4 and TSH levels were measured by the chemiluminescent immunoassay using Beckman Coulter DxI 800 immune-analyzer with original reagents.

Table 1. Characteristics of the groups

	Graves' disease				Thyroiditis				*p* value
	Min	Max.	Median	Mean ± SD	Min	Max.	Median	Mean ± SD	
Age (years)	15	74	38	39.14 ± 14.18	16	72	37	38.58 ± 16.24	0.748
FT3 (ug/ml)	4.43	32.55	10.24	12.24 ± 6.78	3.79	16.44	5.48	6.35 ± 2.64	**0.001**
FT3I	1.01	7.40	2.32	2.76 ± 1.50	0.86	3.74	1.10	1.42 ± 0.61	**0.001**
FT4 (ng/dl)	1.12	7.77	2.79	3.24 ± 1.71	1.76	7.77	2.34	2.81 ± 1.30	0.389
FT4I	0.66	4.77	1.68	1.91 ± 1.01	1.04	4.57	1.37	1.65 ± 0.76	0.392
TSH (U/ml)	0.01	0.01	0.01	0.01 ± 0.01	0.01	0.10	0.01	0.02 ± 0.02	**0.036**
FTHI	1.02	3.28	1.34	1.46 ± 0.37	0.48	0.99	0.91	0.87 ± 0.12	**0.001**

FT3 = Free T3, FT3I = FT3 index, FT4 = Free T4, FT4I = FT4 index, TSH = Thyroid stimulating hormone, FTHI = free thyroid hormone index, Min = Minumum, Max = Maximum, SD = Standard Deviation

Statistical Analysis

The data of our study were uploaded to SPSS 22.0 program and Man Whitney U test was used for the evaluation of the data as it was not possible to perform parametric test assumption (Kolmogorov-Smirnov) and the level of significance was accepted as 0.05.

RESULTS

The findings of the patient groups are shown in table 1.No statistically significant difference was found between the Graves'disease group and the thyroiditis group in terms of age, FT4, and FT4 index (p = 0.748, p = 0.389 and p = 0.392, respectively) (Table 1). When the groups were compared in terms of TSH, FT3 and FT3 index, statistically significant difference was found (p = 0.036, p = 0.001 and p = 0.001, respectively) (Table 1), however no differentiating threshold was found. When the groups were compared in terms of FTHI, the difference was found statistically significant (p = 0.001) (Table 1) (Figure 1). FTHI was above 1 in all patients in Graves'disease group whereas it was found below 1 in all patients in thyroiditis group (Fig. 1).

DISCUSSION

If a patient with moderate to severe hyperthyroidism and has a symmetrically enlarged thyroid gland and a new-onset ophthalmopathy, these are sufficient for Graves'disease diagnosis, and no further analysis are required for a differential diagnosis for hyperthyroidism. When there is a doubt about the diagnosis, the radioactive iodine uptake (RAIU) test should be performed to differentiate from the causes of thyrotoxicosis. RAIU test is generally high in Graves'disease. RAIU test is found close to zero in painless, postpartum or subacute thyroiditis cases, excess thyroid hormone intake or in new excess iodine intake cases.

In technetium scintigraphy (TcO4), pertechnetate captured but not organified by thyroid is used. While this results in a low range of normal uptake and high background activity, total body radiation exposure is less than for 123I scintiscans; either type of scan can be useful in determining the etiology of hyperthyroidism in the presence of thyroid nodularity [6].

Subacute thyroiditis is generally painful and the gland is stiff in palpation. Erythrocyte sedimentation

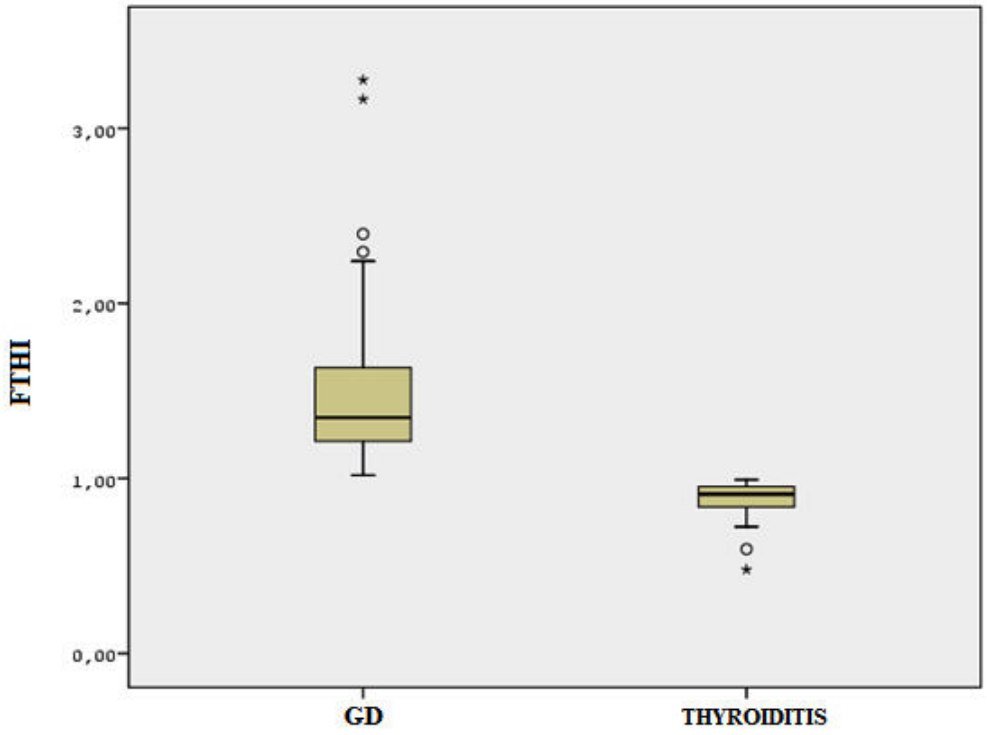

Fig. 1. Comparison of groups according to free thyroid hormone index. GD = Graves' disease, FTHI = Free thyroid hormone index

rate is > 50 mm/h almost in all and sometimes above 100 mm/h. In patients with painless thyroiditis, there is a self or family history of autoimmune thyroid disease, and it is generally observed during postpartum period. There is anti-TPO antibody positivity at a low or moderate level [8].

The use of ultrasonography for the differential diagnosis of thyrotoxicosis is disputable. However, during pregnancy and breastfeeding period, in case of new iodine exposure while RAIU test is contraindicated, color flow Doppler ultrasonography may assist in diagnosing thyroid hyperactivity and to differentiate Graves'disease from destructive thyroiditis [9].

An alternative method to differentiate Graves'disease is measuring the TSH receptor antibody (TRAb). This approach is used in the absence of thyroid scintigraphy and uptake or when these are contraindicated. TRAb may also be measured in patients with postpartum thyroiditis but it shows Graves'disease in high titers [6, 10].

In the absence of thyroid scintigraphy and uptake or when these are contraindicated, the ratio of total T3 and total T4 may be useful in evaluating the etiology of thyrotoxicosis. As T3 synthesis from the hyperactive gland is more than T4, this ratio (ng/mcg) is > 20 in GD and < 20 in painless or postpartum thyroiditis [11]. ATA/AACE guidelines recommend TRAb measurement and total T3/total T4 ratio as an alternative method for the diagnosis of GD in the absence of thyroid scintigraphy and uptake or when these are contraindicated [6]. As serum thyroxine-binding globulin may affect many conditions in an unfavorable manner, total T4 and T3 measurements may be affected.

Today, free thyroid hormone (FT4 and FT3) measurement are used as gold standard test for the diagnosis of thyrotoxicosis [11]. TSH receptor antibody measurement is not performed in many centers, it is expensive and the results take time. In this study, we intended to perform a differential diagnosis for these two conditions by checking the increase ratio of free thyroid hormones.

In our study, we analyzed how much FT3 and FT4 was increased compared to ULN and the ratio of these increases. There was a significant difference between the groups in terms of FT3 and FT3 index, but there was no differentiating threshold value for the diseases. There was no difference between the groups in terms of FT4 and FT4 index. In our study, FT3 index increased more than FT4 indexin all GD patients and FTHI was above 1. On all thyroiditis patients FT4 index increased more than FT3 index and FTHI was below 1.

CONCLUSION

As a result, we demonstrated that we could perform a differential diagnosis for Graves'disease and thyroiditis by only checking the increase ratios in free thyroid hormones. The increase in the free thyroid hormone values in the absence of thyroid scintigraphy and uptake or when these are contraindicated may be used as an alternative method for the differential diagnosis of Graves'disease. This is a new finding but due to the limited number of patients in our study, there is a need for studies with more patients.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2020;6(4):319-325 Original Article

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Determination of error level of ultrasonographic fetal weight estimation according to the seniority of residents in obstetrics and gynecology

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ABSTRACT

Objectives: We consider the difference between estimated fetal weight and birth weight through the measurement according to the seniority of the residents in obstetrics and gynecology. In this study, we aimed to determine the fallibility of the residents according to their seniority years.

Methods: This research was planned as a prospective and approved by the Ethics Committee Ultrasonographic measurements were performed with ultrasound device and the estimated fetal weight was calculated with Hadlock 4 (BPD, HC, AC, FL) formula. Measurements were performed by the residents in the first, second, third and fourth year of training and repeated by the same specialist for each patient. Only those who gave birth within 48 hours of the ultrasonographic measurements were included in the study.

Results: A total of 392 pregnant women were included in the study. Ninety-eight pregnant women were examined by 1st year resident, 100 pregnant by 2nd year resident, 93 pregnant by 3rd year resident and 101 pregnant by 4th resident. Largest difference between the estimated fetal weight and birth weight was performed by the fourth year resident with 125.06 ± 247.40 grams.

Conclusions: The estimated fetal weight by ultrasonography has an important place in obstetric practice and it may vary according to the years of seniority of the resident. For this reason, ultrasonography should be used effectively and accurately during the training of the residents in the centers of education in obstetrics and gynecology and it is essential that the residents learn the ultrasound examination properly and completely.

Keywords: fetal weight, ultrasonography, resident, training, estimation

For over 40 years, evaluation of the fetus and fetal weight estimation by ultrasonography has become routine in the obstetric practice [1, 2]. Fetal growth is monitored by measurement of biometrical parameters such as biparietal diameter (BPD), femur length (FL), head circumference (HC) and abdomen (AC) circumference [3]. Several methods are used to calculate the estimated fetal weight(EFW) and some or all of the parameters such as BPD, FL, HC, AC are included in the EFW calculation [2, 4, 5]. By ultrasonographic fetal evaluation macrosomia, intrauterine growth retardation, amniotic fluid anomalies and fetal malformations can be determined. Average birth weight is an important parameter that may cause neonatal morbidity and mortality. According to fetal weight estimates, follow-up or birth decision can be given for the fetus

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[6, 7]. In addition, the fetal weight estimation is helpful for the clinician in difficult cases such as macrosomic infants and determination of the route of delivery in terms of cephalopelvic disproportion [8]. Making the ultrasound measurements in the wrong plane or section, maternal obesity and amount of amniotic fluid affect the estimated fetal weight calculation [2, 5].

Fetal weight estimation, which is commonly used in obstetric practice, requires an effective ultrasonography. Therefore, effective and correct use of ultrasonography during residency training is gaining importance.

Although there are studies in the literature comparing the estimated fetal weight with the birth weight, there is no study comparing the differences in measurement according to the seniority of the residents in obstetrics and gynecology [2, 4, 9].

In this study, considering the difference between estimated fetal weight and birth weight, we aimed to determine the fallibility of the residents according to their seniority years.

METHODS

This research was planned as a prospective and approved by the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital (Acceptance no: 2011-KAEK-25 2018/09-26). Study included women who gave birth in Bursa Yüksek İhtisas Training and Research Hospital, Obstetrics and Gynecology Clinic between 15.09.2018-15.11.2018. All participants were informed and their consent was obtained. Multifetal gestations and pregnancies with fetal anomaly, systemic diseases, preeclampsia or gestational diabetes were excluded in the study. Ultrasonographic measurements were performed with GE Voluson Pro 730 (USA) brand ultrasound device and the estimated fetal weight was calculated with Hadlock 4 [Log10 BW= 1,326–0,00326 (AC) (FL) + 0,0107 (HC) + 0,438 (AC) + 0,158 (FL)] formula. Measurements were performed by the residents in the first, second, third and fourth year of training and repeated by the same specialist for each patient. Only those who gave birth within 48 hours of the ultrasonographic measurements were included in the study. Measurements of birth weights of newborns were performed within the first hour after delivery. Maternal age, gravida, parity and body mass index (BMI) were determined.

BPD measurement was performed in the midline of the falx cerebri, in which the thalamic nuclei were observed symmetrically on both sides of the falx, from the outer edge of the anterior parietal bone to the inner edge of the posterior parietal bone. In the same plan, HC measurement was performed simultaneously. AC measurement was performed in the transverse plane where vertebras, portal vein and stomach were seen, including echoes of the skin from the outer edges of the section. FL measurement was performed after the femoral diaphysis was clearly visualized and the distal epiphysis and femoral head were not included in the measurement.

Statistical Analysis

Statistical analysis of the data was done by SPSS software version 19.0 (Statistical Program for Social Sciences, Chicago, IL, USA). Mean +/- standard deviation values were used in descriptive statistics of the data. Distribution of the variables was checked by Kolmogorov-Smirnov test. In the comparison of the groups, Student normals t test was used when the data shows normal distribution, whereas Mann Whitneyy U test was used when the data were not normally distributed. $p < 0.05$ was statistically significant.

Tablo 1. Demographic data of patients

	N	Minimum	Maximum	Mean ± Standart deviation
Age (years)	392	15	44	26.98 ± 5.86
Gravida	392	1	8	2.37 ± 1.42
Parity	392	0	5	1.16 ± 1.21
Body mass Index (kg/m²)	392	20.81	44.44	28.89 ± 3.86

RESULTS

A total of 392 pregnant women were included in the study. Ninety-eight pregnant women were examined by 1st year resident, 100 pregnant by 2nd year resident, 93 pregnant by 3rd year resident and 101 pregnant by 4th year resident. Demographic data of patients are given in Table 1. Mean age of the patients was 26.98 ± 5.86. Estimated weights of the fetuses and birth weights and the difference between these two values are shown in Table 2. Mean difference between estimated fetal weight and birth weight was calculated as 64 ± 215.99 grams. Table 3 shows the measurement differences of the residents according to their seniority. Largest difference between the estimated fetal weight and birth weight was performed by the fourth year resident with 125.06 ± 247.40 grams. When the measurements were compared, we determined that the difference between the values of the 2nd year resident and the fourth year resident (p = 0.007) and the difference between the values of the 3rd year and the fourth year resident (p = 0.006) were statistically significant (see Table 4).

Table 2. Estimated weight and actual weight values of fetuses

	N	Mean ± Standart deviation	Minimum	Maximum
Estimated fetal weight (EFW) (gram)	392	3208.85 ± 553.15	810	4600
Birth weight (gram)	392	3144.74 ± 565.77	840	4630
Difference between EFW and Birth weight (gram)	392	64 ± 215.99	-900	836

Table 3. Weight measurement differences of the residents according to their seniority

	N	Mean ± Standart deviation	95% confidence interval for average		Minimum	Maximum
			Lower Limit	Upper Limit		
1th year resident	98	77.35 ± 262.40	24.74	129.96	-650	547
2nd year resident	100	27.24 ± 189.46	-10.35	64.83	-410	670
3th year resident	93	23.60 ± 114.48	0.02	47.18	-900	250
4th year resident	101	125.06 ± 247.40	76.22	173.91	-565	836
Total	392	64.11 ± 215.99	42.66	85.56	-900	836

DISCUSSION

Estimated fetal weight is determined automatically by ultrasound device after the measurement of BPD, HC, AC and FL parameters based on various formulas [3]. There may be a difference between the estimated fetal weight and actual birth weight. This may be due to fetal and maternal reasons, and may differ according to the clinician who applied ultrasonography [1, 2, 9, 10]. In our study, we determined the actual birth weights of newborns and the estimated fetal weight measured by ultrasonography by residents in obstetrics and gynecology, and compared the differences between them according to the seniority of the residents.

In a study by Özçam *et al*. [2], it was evaluated the

Table 4. Comparison of weight differences between groups

Senior groups by years		Mean± Standart deviation	*p* value	95% confidence interval for average	
				Lower limit	Upper limit
1th year resident	2nd year resident	50.11 ± 30.23	0.59	-30.07	130.30
	3th year resident	53.75 ± 30.79	0.49	-27.91	135.42
	4th year resident	-47.71 ± 30.16	0.68	-127.70	32.28
2nd year resident	1th year resident	-50.11 ± 30.23	0.59	-130.30	30.07
	3th year resident	-3.63 ± 30.64	1.0	-77.63	84.90
	4th year resident	97.82 ± 30.01	0.007*	-177.41	-18.24
3th year resident	1th year resident	-53.75 ± 30.79	0.49	-135.42	27.91
	2nd year resident	-3.63 ± 30.64	1.0	-84.90	77.66
	4th year resident	-101.46 ± 30.57	0.006*	-182.54	-20.39
4th year resident	1th year resident	47.71 ± 30.16	0.687	-32.28	127.70
	2nd year resident	97.82 ± 30.01	0.007*	18.24	177.41
	3th year resident	101.46 ± 30.57	0.006*	20.39	182.54

*$p < 0.05$

Table 5. Predictions of all residents according to BMI of patient

	n	Mean ± Standart deviation	95% confidence interval for average		Minimum	Maximum
			Lower Limit	Upper Limit		
Normal	60	33.08 ± 225.08	-25.06	91.22	-450	525
Overweight	176	71.20 ± 228.17	37.25	105.14	-650	670
Obese	156	68.04 ± 197.91	36.74	99.34	-900	836
Toplam	392	64.11 ± 215.99	42.66	85.56	-900	836

effect of parity, maternal body mass index, weight gain during pregnancy, stage of delivery and amniotic fluid content on estimated fetal weight by ultrasonography. In this retrospective study of 100 pregnant women, it was determined that the parameters such as gender of the fetus, maternal parity, stage of delivery, preconceptional BMI, weight gain during pregnancy were not statistically significant in estimated fetal weight ($p < 0.05$). In addition, it was found that ultrasonographic estimation of fetal weight was closely correlated with actual birth weight in pregnant women with oligohydramnios and / or perfused amniotic membranes [2]. In our study, we found that the difference between ultrasonographic fetal weight estimation and actual birth weight decreased with the increase of seniority years of the residents. As an exception, as a result of the measurements made by the 4th year resident, we found that the estimated fetal weight increased and the difference between ultrasonographic measurements and the actual birth

Tablo 6. Comparison of groups according to BMI

		Mean ± Standart deviation	*p* value	95% confidence interval for average	
				Lower limit	Upper limit
Normal	Overweight	-38.12 ± 32.31	0.71	-115.80	39.56
	Obese	-34.96 ± 32.83	0.86	-113.90	43.98
Overweight	Normal	38.12 ± 32.31	0.71	-39.56	115.80
	Obese	3.15 ± 23.76	1.0	-53.98	60.30
Obese	Normal	34.96 ± 32.83	0.86	-43.98	113.90
	Overweight	-3.15 ± 23.76	1.0	-60.30	53.98

weight was enlarged. When the measurement were compared, we determined that the difference between the values of the 2nd year resident and the fourth year resident (p = 0.007) and the difference between the values of the 3rd year and the fourth year resident (p = 0.006) were statistically significant.

In our study, we used Hadlock 4 formula in fetal weight estimation. In the literature, there are studies about how accurate the various formulas predict the fetal birth weight. In a study by Blue *et al*. [9], they compared the Hadlock method with the racial / ethnic standard method of the Unice Kennedy Shriver National Institute of Child Health and Human Development. In the study, 1,514 pregnant women were evaluated and the Hadlock method was found to be superior to the racial/ethnic standart method of Unice Kennedy Shriver's National Health and Human Development method [9]. In a study conducted by Energin [5], 2-dimensional and 3D ultrasound measurements, and the accuracy of the estimated fetal weight (EFW) formulas used in these measurements were evaluated. In this study, 165 pregnant women were evaluated using the Hadlock I (BPD, AC, FL), Hadlock II (BPD, HC, AC, FL), Shepard (BPD, AC) formulas to determine EFW in 2-dimensional (2D) ultrasonography. In 3D ultrasonography, Lee I (TVol), Lee II (TVol, AC) and Lee III (TVol, AC, BPD) formulas were used for EFW measurements. No significant difference was found between the measurements performed with Lee I, Hadlock II, Hadlock I and newborn birth weights. They found a statistically significant difference between newborn birth weights and measurements performed with Lee II, Lee III and Shephard formulas. As a result of the study, it was clinically possible to use 3D ultrasonography in the calculation of EFW [10].

In another study by Blue *et al*. [9], Hadlock formula was compared with new methods in the estimation of fetal weight. In this study, Intergrowth-21st (INTG) and Salomon technique were compared with the Hadlock formula, and they found that the Hadlock formula was more successful in the determination of small for gestational age (SGA) fetuses.

In a different study, Pretscher *et al*. [1], evaluated the success of sonographic measurements in predicting poor outcomes of pregnancy. However, the results of the study showed that such a prediction is not possible with ultrasonographic measurements [1]. In our study, we calculated the estimated fetal weight using the Hadlock formula and BPD, HC, AC, FL parameters. We found the mean difference between the estimated fetal weight and the actual newborn birth weight as 64 ± 215.99 grams.

In a study of 165 pregnant women, Energin [5] evaluated the factors affecting the estimated fetal weight measured by ultrasonography. Results of the study showed that gravida, parity, sex of the fetus, presence of meconium in amniotic fluid and fetal presentation did not have any effect on fetal weight. In addition, the study also reported that maternal obesity had no effect on fetal weight [5]. In contrast, another study by Özen *et al*. [6] found that maternal obesity had a negative effect on fetal weight

estimation. In our study, we found that the margin of error in obese patients was higher than patients with normal weight. The comparison of the groups according to the difference between the estimated fetal weight was not statistically significant.

In our study, we evaluated the difference between the estimated fetal weight and the actual newborn birth weight according to the seniority of the residents in obstetrics and gynecology. A similar study was not found in the literature. We found that the difference between ultrasonographic fetal weight estimation and actual birth weight decreased with the increase of seniority years of the residents. As an exception, as a result of the measurements made by the 4th year resident, we found that the estimated fetal weight increased and the difference between ultrasonographic measurements and the actual birth weight was enlarged. Possible reason for that, is the decrease in the error margin of the measurements with the increase of the experience of the residents. Increase in the error of the 4th year resident may be related to the fact that the residents in their last year oftenly providing the coordination and organization, and the patient's first examination including ultrasound measurements is made by the residents in 1st or 2nd year.

In our study, it was also shown that with the increase in BMI in patients, estimated fetal weight averages increased and high BMI had a negative effect on EFW. Fact that the data were not found statistically significant in this study may be due to the low number of cases (see Tables 5 and 6).

CONCLUSION

In conclusion, the estimated fetal weight by 2D or 3D ultrasonography has an important place in obstetric practice and it may vary according to the years of seniority of the rezidents. For this reason, ultrasonography should be used effectively and accurately during the training of the residents in the centers of education in obstetrics and gynecology and it is essential that the residents learn the ultrasound examination properly and completely.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Ethics statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Scientific responsibility statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

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Clinical and electrophysiological follow-up of modafinil treatment for multiple sclerosis patients with fatigue symptom

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ABSTRACT

Objectives: In our study, we investigated the effects of modafinil therapy on clinical and neurophysiological tests of multiple sclerosis (MS) patients with fatigue.

Methods: The study was performed on 18 MS patients (16 females, 2 males) at Uludağ University School of Medicine, Department of Neurology, who are followed up according to Mc Donald's criteria, who had 36 points or above based on the fatigue assesment scala (FAS), whose Beck depression inventory points were 16 and below, whose thyroid, liver and renal functions were evaluated as normal, and who had no systemic disorder. All patients had neurological examination and their expanded disability status scale (EDSS), fatigue impact scala (FIS) and multiple sclerosis quality of life (MSQoL-54) were evaluated. Somatosensory evoked potential (SEP), visual evoked potential (VEP), brainstem auditory evoked potential (BAEP), visual event related evoked potential (visual P300) were performed in our neurophysiology laboratory. After that the patients were given modafinil 100 mgr 1x1 (morning) for 1 week, the following weeks 2x1 (morning and noon). At the end of the 6 weeks of therapy the patients were called to the neurology polyclinic, and their neurological examinations, EDSS, FIS, MSQoL-54, SEP, VEP, BAEP and visual P300 were repeated.

Results: When the patients' previous and subsequent FIS and MSQoL-54 total scores were compared, a significant statistical difference was found. When all 3 subgroups of FIS (consciousness, physical and social) were evaluated after the modafinil therapy, a significant statistical decrease in previous and successive scores were found. It is found out that modafinil therapy improves life quality which is evaluated due to MSQoL-54 ($p < 0.05$). A significant statistical relation between the number of MS disease attacks and the three subgroups of MFIS was not figured out ($p > 0.05$). There were no statistically significant relation between the FAS, EDSS and Beck depression inventory scores before the modafinil therapy had been applied ($p > 0.05$). There was a statistically correlation between Beck depression inventory score and FIS's social subgroup ($p = 0.017$). When the patient's SEP, VEP, BAEP, visual P300 average test values before and after the modafinil therapy were compared, a statistically significant difference was not observed.

Conclusions: In our study, it is found that modafinil therapy, which is used against fatigue, one of the MS disase's most common symptom, has a positive impact on MS life quality and patients' clinical symptoms of fatigue, although it has no effect on patients' evoked potential methods (BAEP, SEP, VEP, visual P300) performed in neurophysiology laboratory.

Keywords: multiple sclerosis, fatigue, modafinil, evoked potential, fatigue severity scala

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Although multiple sclerosis (MS) is a clinically heterogeneous neurological disease, it is difficult to diagnose the disease due to the diversity of its symptoms, its fluctuating nature, and its heterogeneity [1]. Despite its disadvantages in the evaluation of cognitive deterioration and upper extremity functions as demonstrated in clinical MS studies, the expanded disability status scale (EDSS) is used as the primary measurement method of disability in MS [2].

Fatigue is today recognized as the most prevalent symptom of MS. MS-derived fatigue is different from the usual fatigue that follows strenuous activities, and it is believed that such fatigue is specific to MS. Freal *et al*. [3], who were the first to study fatigue complaints of MS patients, reported that 75-90% of the patients included in their sample complained about fatigue.

The symptoms and consequences associated with fatigue include physical fatigue, mental fatigue, absence of motivation, concentration difficulty, incapability of fulfilling tasks, sense of depression, sense of anxiety, tiredness after sleep, general and specific muscle weakness, diminished performance at home and/or at work, pain and/or physical ailments, and sleep disorders [4].

This study aims to investigate the qualitative effect of modafinil treatment on fatigue assessment scales and on the quality of life scale, and the quantitative effect of the said treatment on the measurement of evoked potentials and on clinical and neurophysiological tests. To the best of the researchers' knowledge, this is the first study to analyze the effect of modafinil treatment administered for MS-related fatigue, on somatosensory evoked potential (SEP), visual evoked potential (VEP), brainstem auditory evoked potential (BAEP), and all of the event-related endogenous potentials.

METHODS

A total of 18 patients (16 females and 2 males), who had received follow-up care for 6 months at Uludağ University School of Medicine, Department of Neurology due to MS diagnosis, were included in the study after they had given their informed written consent to participate. The study was approved by the local ethics committee. To be included in the study, patients had to have no systemic disease, no pathology according to thyroid function tests, liver function tests, and kidney function tests, and they had to have complaints about fatigue and scores of ≥ 36 and ≤ 16 on the fatigue assessment scale (FAS) and Beck's Depression Inventory, respectively. Patients who had started to undergo antidepressant treatment within the last 3 months and/or who had had a seizure within the last 4 months were excluded from the study.

The results from the EDSS, the fatigue impact scale (FIS), and the MS Quality of Life Scale-54 (MSQoL-54) of the patients included in the study were evaluated as part of the neurological examination. The modafinil treatment of the patients started with the administration of a 100 mg dose of 1x1 tablet (morning) in the first week and a 100 mg dose of 2x1 tablet (morning and noon) in the weeks that followed. Prior to the modafinil treatment, SEP, VEP, BAEP and visual event-related endogenous potential (Visual P300) were applied on the patients in the neurophysiology laboratory. At the end of week 6 of the treatment, the patients visited the outpatient department and underwent a neurological examination again based on the assessment of EDSS, FIS, MSQoL-54, SEP, VEP, BAEP, and Visual P300.

Disability Assessment

The participants' level of neurological impairment was assessed using the Kurtzke EDSS. Impairment in 8 functional systems is measured with this scale, with most of the scores in the functional system being assessed in a range from 0 to 6, where 0 showing normal neurological examination, whereas 10 indicates MS-related death [2].

Fatigue Assessment Scale (FAS)

Fatigue symptoms were scaled with FAS, which is a nine-part scale used to evaluate the overall effect of fatigue on daily activities. Each part is scored according to a seven-point Likert-type scale, where 1 is never agree and 7 is completely agree. The FAS score is calculated by summing up or averaging out the scores of the nine parts. FAS is effective for distinguishing patients with fatigue complaint who need treatment and those who do not require treatment. Moreover, it is used to detect the effects of the treatment administered to patients with fatigue symptoms [5].

Fatigue Impact Scala (FIS)

The FSS, which evaluates physical, psychological, and cognitive functions, is more detailed than FAS. There are 10 items under the cognitive component, 10 items under the physical component and 20 items under the psychosocial component. Responses to each item range from 0-3 (0: no problem, 3: very big problem) [6].

Quality of Life Scale (MSQoL-54)

For this scale, 18 MS-related questions were added to the original 36-Item Short Form Health Survey Questionnaire (SF-36), which was developed from the Medical Outcome Study and is used for all chronic diseases (10). SF-36 includes 36 items under 8 scales. Of these 36 items, 10 are related to physical function, 4 to the role of physical function, 2 to body pain, 5 to general health, 4 to liveliness, 2 to social function, 3 to the role of emotional function, and 5 to mental health. Vicrey *et al*. [7] added 18 items to this scale, of which 4 are related to health-related stress, 4 to sexual function, 1 to satisfaction in sexual function, 2 to quality of life, 4 to cognitive function, 1 to energy, 1 to pain, and 1 to social function.

Electrophysiological Procedures

The patients' SEP, VEP, BAEP, and P300 were recorded at room temperature (22 ºC) in the Uludağ University Schol of Medicine, Neurophysiology Laboratory. A Medelec/TECA "Sapphire" brand device was used to conduct these measurements after performing a complete skin cleansing process. Electrode impedances were kept below 5 kOhm in all of the applications.

The waves that emerged in the first 10 ms were recorded with BAEP following an 80-85 dB monoaural click stimulus. The click was applied 60 decibels above the threshold of hearing to one, while the other ear was masked by noise. Active electrode and reference electrode were placed on point CZ and ipsilateral mastoid (M1 and M2), respectively, during recording. Analysis duration was set as 100 ms, with the polarity alternans and frequency limits placed at 100-200 Hz.

Recording was performed on the occipital by stimulating the eyes with VEP through a checkerboard-pattern reversible stimulus. The color of the black-white checkerboard-pattern squares on the screen changed every 20 ms. The patients were seated 90 cm from a TV screen, whereon the stimuli, activated 3 cycles per second, were watched. Superficial electrodes were used for recording. Active electrode and reference electrode were put on point OZ and point FZ, respectively. Frequency limits were set to 1-100 Hz, while the analysis duration was set as 250 ms. The middle part of the screen was marked to ensure visual fixation. The whole screen was able to be seen at a 23° angle, while a square on the screen was able to be seen at a 1° angle. As one eye was stimulated, the other eye was closed with an eye patch. Median SEP (mSEP) was obtained through electrical stimulation of the right and left median nerve. The electrical stimulation was applied at a frequency of three 50 ms per second using a sensitivity just over the motor threshold. The records were attained from the C3 contralateral cortex region.

Tibial SEP (tSEP) was obtained with the electrical stimulation of n. tibialis posterior from ankle. Successive electrical stimulation was applied at a frequency of four 100 ms per second using a sensitivity just over the motor threshold. Recordings were performed in the foot region (Cz). Frequency limits were set as 10-2000 Hz, while the analysis duration was set as 100 ms.

Event-related endogenous potentials are a type of evoked potential that forms as a response to an event outside or a stimulus. It occurs when a person distinguishes two stimuli of different qualities whose recurrence intervals are variable (target and non-target) when he/she pays attention to the stimuli. P300, which was used to assess the mental functions, is the most well-known wave with respect to event-related endogenous potentials [8]. During P300 assessment, the target stimulus was sent to both eyes at various intervals following the routine stimulation repeated once a second. Active recording was performed based on point Pz. The duration of routine stimulations and target stimulations were 2 ms and 30 ms, respectively. Routine stimulations constituted 85% of all stimulations, while target stimulations constituted 15% of all stimulations. The average analysis duration was 1 s, and the lower and upper frequencies were applied within a range of 0.1-50 Hz.

Depression Assessment

The patients were assessed with Beck's

Table 1. Demographic and MS-related information

Number of patients (n)	18
Female/male, n (%)	16 (88.9)/ 2 (11.1)
Mean age (mean ± SD) (years)	40.5 ± 10.4
Mean age of onset of disease (mean ± SD) (years)	32.3 ± 8.4
Clinical type of MS, n (%)	
Relapsing remitting	15 (83.3)
Secondary progressive	2 (11)
Rrelapsing progressive	1 (5.6)
Mean duration of disease (mean ± SD) (years)	8.1 ± 5.9
Mean EDSS score (mean ± SD)	1.8 ± 1.1

MS = multiple sclerosis, EDSS = expanded disability status scale, SD = standard deviation

Depression Inventory to ascertain their depressive symptoms. Beck's Depression Inventory consists of 21 items, with each item having four response options. Every item is scored from 1 to 4, and scores ≥ 17 are evaluated as indication of depression [9]. The patients who received scores of ≥ 17 were excluded from the study .

Statistical Analysis

Statistical assessment of the study data was performed with SPSS programme for Windows. A post hoc power analysis was conducted using a medium effect size, based upon findings of the present study. A medium effect size was obtained by comparing mean Physical dimension scores which were calculated from before treatment (14.1 ± 4.6) and after treatment (8.5 ± 6.3) terms for 18 participants. Using this effect size (d = 0.75) with a sample size of 18 participants, achieved power was estimated as 81% at the significance level of α= 0.05. The median (minimum-maximum) was calculated for all data in cases where the mean standard deviation (mean ± SD) was needed. Paired t-test and Wilcoxon signed-rank test were used to compare the pre-treatment and post-treatment scale scores. Correlation analyses were conducted for the correlations between the scale scores and Pearson or Spearman correlation coefficients were reported. A significance level of $p < 0.05$ was set for all statistical analyses.

RESULTS

The mean age of the patients was 40.5 ± 10.4 years (males: 317 years; females 41.6 ± 10.3 years). The mean age of onset of MS symptoms was 32.3 ± 8.4 years, while the mean duration of disease was 8.1 5.9 years. In terms of the clinical type of MS, 15

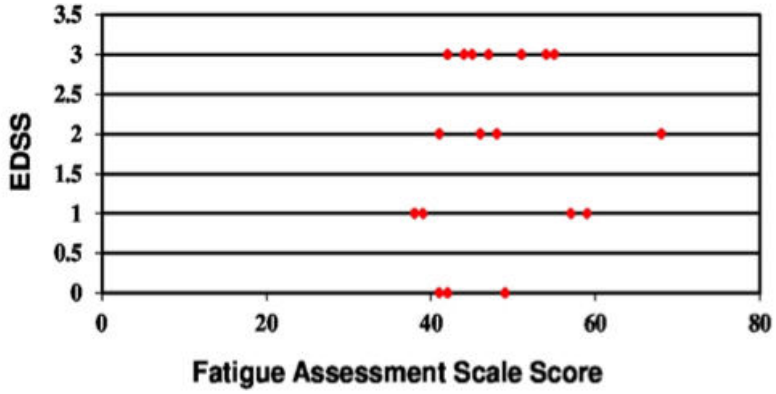

Fig. 1. Relationship between the expanded disability status scores and fatigue assessment scores of the patients.

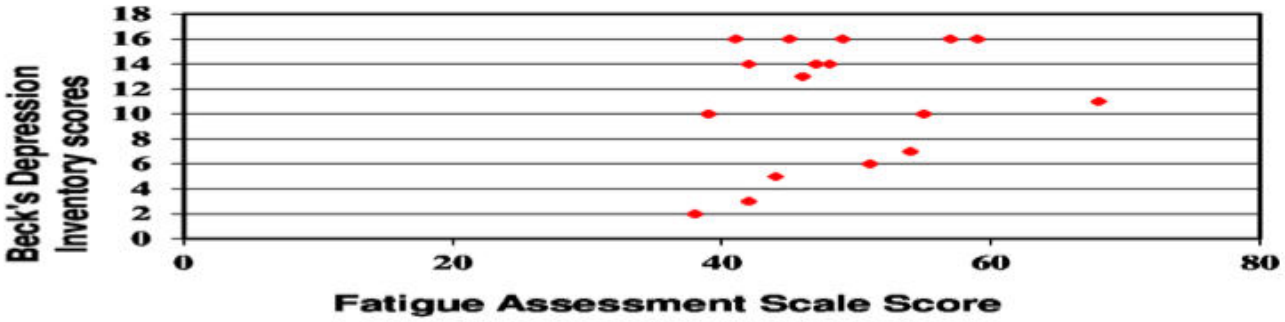

Fig. 2. Relationship between the scores on Beck's Depression Inventory and Fatigue Assessment Scale.

patients had relapsing remitting, 2 patients had secondary progressive, and 1 patient had relapsing progressive. The mean EDSS of the patients was 1.8 ± 1.1 (Table 1).

Among the patients included in the study, 15 (83.3%) were using an immunomodulator, while 3 (16.7%) were not; of the 15 patients who were using an immunomodulator, 5 (27.8%) had been on it for one year, 5 (27.8%) for two years, 2 (11.1%) for three years, 2 (11.1%) for four years, and 1 (5.6%) for five years. Seven patients were using beta interferon 1 b 0.3 MG (9.6 MIU) subcutaneous every other day, 3 patients were using beta interferon 1a 44 mcg (12 MIU) subcutaneous three times a week, 4 patients were using glatiramer acetate 20 mg subcutaneous every day, and 1 was using interferon beta 1 a 30 mcg (6 MIU) intramuscular once a week.

Nine patients had been on antidepressants for at least for three years, while nine patients had not been taking antidepressants. Regarding MS onset symptoms, 4 patients had optic neuritis, 8 patients had pyramidal signs, 2 patients had cerebellar signs, 2 patients had cerebellar and pyramidal signs, and 2 patients had sensual signs. Regarding relapses, 2 patients had one, 6 patients had two, 4 patients had three, 3 patients had four, 1 patient had five and 2 patients had 6. Within the last two years, 6 of the patients did not have any relapse, while 10 patients and 2 patients had one and two relapses, respectively.

There was a negative correlation between age and the pre-treatment score on the Beck's Depression Inventory (Spearman correlation coefficient = -0.716, $p = 0.001$). No statistically significant relationship was found between the pre-treatment scores on the FAS and the EDSS (Spearman correlation coefficient = 0.210, $p > 0.05$). (Fig. 1). No statistically significant relationship was found between the pre-treatment scores on the FAS and the Beck's Depression Inventory (Spearman correlation coefficient = 0.369, $p > 0.05$) (Fig. 2).

According to the Wilcoxon rank-sum test, the difference between the pre-treatment scores and post-treatment scores on Beck's Depression Inventory was statistically significant, with the Beck's Depression Inventory scores of the patients being significantly lower after the treatment. ($p < 0.001$) (Table 2). The mean total FAS score of all 18 patients after the treatment (32.7 ± 9.2) was statistically significantly lower than that before the treatment (48.1 ± 7.9). The difference between the total FAS scores was found to

Table 2. Beck's Depression Inventory scores

	Before modafinil treatment	After modafinil treatment	*p* value
Beck's Depression Inventory Score			
Mean ± SD	10.7 ± 5.0	4.7 ± 4.43	**< 0.01***
Median	12	4	
Minimum-maximum	2-16	0-12	

*According to Wilcoxon rank-sum test, SD = standard deviation

Table 3. Relationship between the sub-dimensions of fatigue impact scale before the treatment and after the treatment

	Before the treatment	After the treatment	*p* value
Cognitive dimension			
Mean ± SD	12.8 ± 4.4	8.8 ± 7.5	**0.014***
Median	12.5	11	
Minimum-maximum	6-20	0-20	
Physical dimension			
Mean ± SD	14.1 ± 4.6	8.5 ± 6.3	**0.007***
Median	14	8.5	
Minimum-maximum	5-21	0-21	
Social dimension			
Mean ± SD	30.1 ± 12	16.8 ± 12.5	**0.001***
Median	28.5	18.5	
Minimum-maximum	13-55	0-38	

*Wilcoxon rank-sum test, SD = standard deviation

be statistically significant to the highest degree (Matched-pair t-test, $p < 0.001$).

No statistically significant correlation between age and FAS values was detected (Pearson correlation coefficient = 0.153, $p > 0.05$).

Significantly lower values in the cognitive, physical, and social dimensions of FIS were determined during the post-treatment measurement based on the Wilcoxon rank-sum test. There were significant (+) correlations between cognitive, physical, and social dimensions to the highest degree following the treatment (after the treatment, Spearman coefficients for the relationship between cognitive and physical dimensions = 0.744 ($p < 0.001$), for relationship between cognitive and social dimensions =0.685 ($p = 0.002$) and for relationship between physical and social dimensions = 0.814 ($p < 0.001$)). No statistically significant relationship was found

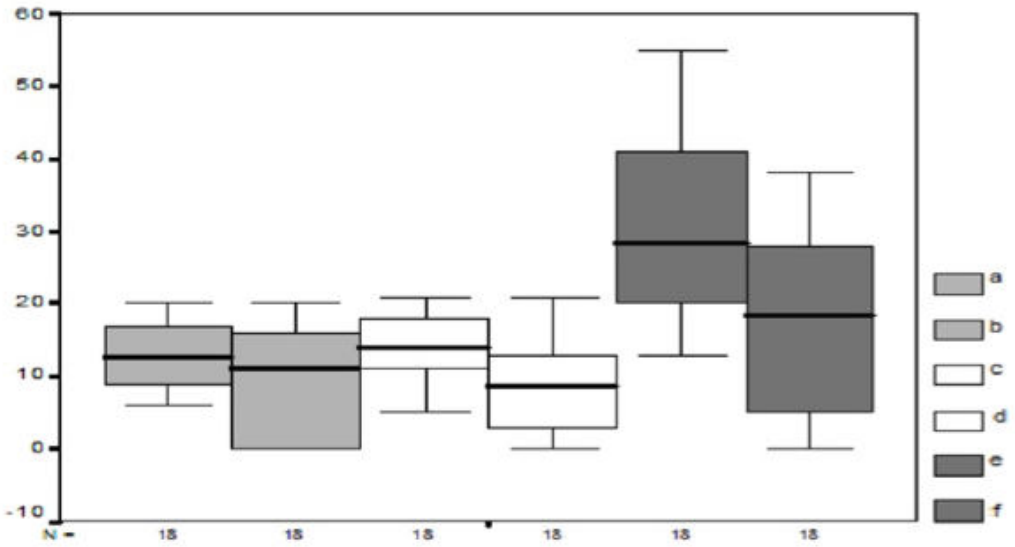

Fig. 3. The relationship between sub-dimensions of the Fatigue Impact Scale. (a) pre-treatment cognitive dimension, (b) post-treatment cognitive dimension, (c) pre-treatment physical dimension, (d) post-treatment physical dimension, (e) pre-treatment social dimension, (f) post-treatment social dimension.

Table 4. Relationship between the sub-dimensions of MS Quality of Life Scale (MSQoL-54) before the treatment and after the treatment

MS Quality of Life Scale (MSQoL-54)	Before the treatment	After the treatment	*p* value
Physical health	52.30 ± 13.01	72.23 ± 13.06	**< 0.001**
Cognitive health	54.25 ± 19.33	69.79 ± 16.39	**0.001**
Change in health	58.33 ± 25.72	73.61 ± 18.13	**0.005**
Sexual function	54.16 ± 21.43	68.05 ± 23.95	**0.008**

between the number of MS relapses and the 3 dimensions on the FIS ($p > 0.05$) (Table 3) (Fig. 3). There was a statistically significant moderate correlation between the score on the Beck's Depression Inventory and the social dimension of the FIS (Spearman correlation coefficient 0.553, $p = 0.017$).

A statistically significant difference was found between pre-treatment values and post-treatment values on the four sub-dimensions of the MSQoL-54. According to the matched-pair t-test, pre-treatment values on physical health and cognitive health were significantly lower than their respective post-treatment values (p values based on matched-pair t-test: physical health; $p < 0.001$, cognitive health; $p = 0.001$). When pre-treatment values and post-treatment values related

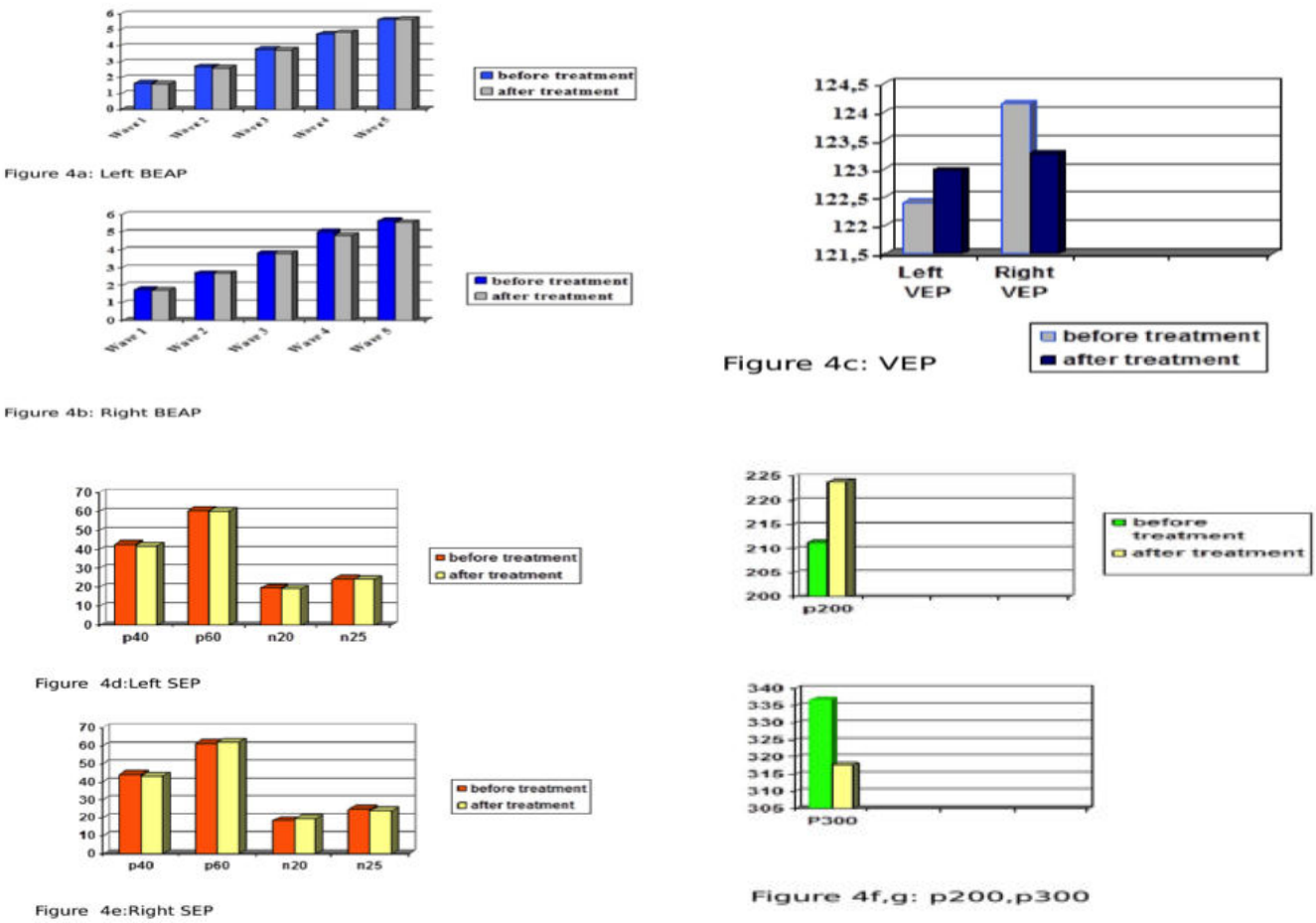

Fig. 4. Evoked potential values attained before the treatment and after the treatment. (a, b) BAEP = brainstem auditory evoked potential, (c) VEP = visual evoked potential, (d, e) SEP = somatosensory evoked potential, (f, g) P200, P300 = visual event related evoked potential..

to the sub-dimensions of change in general health and in sexual functions in one year were compared, post-treatment values were found to be significantly lower (According to Wilcoxon rank-sum test: change in health; $p = 0.005$, sexual function; $p = 0.008$) (Table 4).

Mean right and left VEP values, mean right and left BAEP values, mean lower and upper SEP values, and mean p200 and p300 values of the patients obtained before the treatment and after the treatment were matched. When the evoked potential values were statistically compared based on the matched-paired t-test, no significant difference was observed (Fig. 4).

DISCUSSION

The relationship between the clinical type of MS, physical disability and depression of the patients, and fatigue has been discussed for many years. Neurological impairment and fatigue affect the quality of life of MS patients adversely, as does fatigue and depression, as demonstrated by results from the EDSS [10]. While some studies have shown there to be no relationship between age, gender, duration of disease and fatigue [11-13], others have reported that fatigue increases in parallel with age and longer duration of disease [14-16]. In the present study, no statistically significant relationship was detected between scores on the FSS and the frequency of seizures.

Depression is a symptom which usually accompanies MS, having a prevalence of above 50% [17, 18]. Inconsistent results have been reported in studies examining the relationship between depression and fatigue. Several studies have revealed there to be a moderate [19, 20] or strong [21] relationship, whereas others have found there to be no relationship [22, 23]. For example, in a study by Flachenecker *et al*. [24], which included 151 diseases, the FAS scores of the patients with depression were significantly higher than those of the patients without depression. Although depressive and anxious patients complained about fatigue more, only a weak linear correlation between fatigue and depression and anxiety was revealed [13]. As fatigue is regarded as a feature of depression, overlapping is to be expected. On the other hand, this point emphasizes the importance of defining fatigue clearly. In the present study, no statistically significant relationship was observed between the pre-treatment scores obtained on the Beck's Depression Inventory and the FAS. Treatment of depression in MS may not lead to a reduction in the complaints about fatigue. Mohr *et al*. [25] reported a significant improvement only in global fatigue severity among the four sub-dimensions (global fatigue severity, situation-specific fatigue, results of fatigue, responsivity to rest and sleep) of the fatigue assessment instrument following a 16-week treatment with sertraline. The relationship between fatigue and depression remains unclear [26].

Studies have presented inconsistent results about the correlation between fatigue and EDSS as well. Several studies have determined there to be a positive correlation between these two variables [27, 28], some [11, 24, 29] have found there to be a weak correlation [30, 31] and others have reported there to be no correlation [32, 33]. The differences in the results found in these studies could have resulted from cohort features, the assessment tools used in fatigue measurement, change in neurobehavioral findings with medication, or differences in the designs applied by these studies [34]. In the present study, there was no statistically significant relationship found between fatigue and EDSS, the results of which could be attributed to the low number of patients in the study and the similar EDSS scores of the patients.

Fatigue is worse in progressive MS and worsens apparently when ambulation is affected. However, it should be noted that fatigue is a cause of morbidity, even among patients who do not complain about fatigue [13]. Studies have demonstrated that patients with progressive MS experience fatigue more frequently than patients with relapsing remitting MS [15, 35]. In the present study, an evaluation of the relationship between clinical type of MS and fatigue could not be conducted due to the low number of patients and to the fact that a majority of the patients had relapsing remitting MS.

Fatigue is explicitly related to physical and psychological functional disruption. It has been found that fatigue rises dramatically when walking ability is affected [13]. Detection of high levels of physical fatigue plays a role in predicting an increase in disability in three years [36].

Analyses on quality of life sub-dimensions indicated that both fatigue and depression have a

strong relationship with quality of life due to emotional problems and pain, and that depression has importance in predicting emotional well-being, cognitive function and health distress, regardless of the physical disability and fatigue levels of the patients [10]. Merkelbach *et al*. [37] argue that psychological symptoms are more important than physical disability with respect to fatigue.

Modafinil, amantadine, 4 aminopyridine, antidepressants, and L-carnitine are used for the treatment of MS-related fatigue . In the present study, comparison of the mean total Beck's Depression Inventory and FAS scores of the patients obtained after a 6-week modafinil treatment for overcoming their complaints about fatigue to their initial scores showed that the former were statistically significantly lower. These results implicitly indicate that the treatment of the fatigue symptoms seen in the patients reduced their depressive symptoms as well. The post-treatment values on the four sub-dimensions (physical health, cognitive health, change in health, sexual function) of the MSOoL- 54 were significantly lower than the pre-treatment values of these dimensions, thereby supporting that modafinil treatment was useful for the patients. This outcome suggests that fatigue symptom affects the quality of life of MS patients adversely, and that the treatment of fatigue symptom improves their quality of life. Rammohan *et al*. compared the scores attained on fatigue scales after placebo with the scores found after a 2-week modafinil treatment administered as 200 mg/day and reported there to be an apparent improvement in fatigue symptom following modafinil treatment [38]. A double blind study that comparatively analyzed the use of placebo and modafinil for 8 weeks among MS patients with fatigue determined that administration of modafinil improved not only fatigue symptoms but also attention and manual skill performances [39].

To the best of the present researchers' knowledge, there is no study examining the effect that modafinil treatment for MS-related fatigue has on evoked potentials in MS patients, where the aim is to measure the treatment results quantitatively. The closest study found, in terms of similarity to the present one, was the one conducted by Sangal *et al*., where a visual P300 evoked potential procedure was implemented to detect the response of narcolepsy patients to modafinil treatment; it was reported that such neurophysiological tests are not effective for detecting the response to modafinil treatment earlier [38]. In the analysis conducted in the present study, where BEAP, SEP, VEP, and visual P300 evoked potential methods were used before and after the modafinil treatment of the patients, it was observed that the well-being of the patients after the treatment, which was determined with subjective methods, did not affect the neurophysiological tests.

According to a study which evaluated visual and brainstem auditory-evoked potentials of MS patients on the basis of the presence and severity of fatigue, P100 latency (interocular latency difference) increased significantly when the patients with high fatigue severity were compared to MS patients without fatigue symptom [40]. The same study revealed BAEP anomalies (prolonged interlatency between BAEP 1-3-5 components) among MS patients with moderate and severe fatigue. This result indicates that there are conduction disturbances inside the brain stem, which suggests that the progression rate and disability of these sub-groups are extremely high.

CONCLUSION

Fatigue is a very frequently-seen symptom in MS patients and affects their quality of life. When modafinil, whose use in narcolepsy treatment was approved by the FDA, was administered to the MS patients, it was observed that their fatigue symptoms declined and their quality of life improved as compared to the pre-treatment period. However, the modafinil treatment had no effect on evoked potential procedures when it was applied to treat MS-related fatigue symptoms. Further studies involving more patient groups are required to determine the effect of evoked potential parameters on fatigue symptoms of MS patients and to detect the importance of certain parameters, like electrophysiological reagents.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Effect of anatomic fibula on tibia union and alignment after intramedullary nailing of tibia shaft fractures

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ABSTRACT

Objectives: The effect of an intact or fixated fibula on tibial union and alignment in tibial shaft fractures applied with intramedullary nailing is investigated.

Methods: A retrospective examination was made of 67 patients aged 19-85 years who were applied with intramedullary nailing for a tibial shaft fracture (AO-42) between January 2010 and December 2016. The 44 patients included in the study were separated into 2 groups as those with anatomic fibula (Group 1, n = 12) and those with a fibula fracture which is not fixated (Group 2, n = 32). The patients were evaluated in respect of bone union and malalignment from direct radiographs. Union was evaluated according to the RUST criteria, and the threshold for malalignment was taken as 5˚ in the coronal and sagittal planes.

Results: The patients comprised 24 males and 20 females (M/F: 6/5) with a mean age of 42.7 years (range, 19-76 years). Non-union was observed in 3/12 patients (25%) in Group 1, and in 2/32 (6.3%) patients in Group 2 at 6 months. Malalignment was observed in 1/12 (8.3%) patients in Group 1 (procurvatum) and in 7/32 (21.8%) patients in Group 2, of which 3 (9.3%) were varus, and 4 (12.5%) were valgus. The rate of malalignment was significantly lower in Group 1 than in Group 2.

Conclusions: The results demonstrated that bone union of a tibial shaft fracture is slower in patients with an anatomic fibula compared to those with non-anatomic fibula. Although the anatomic fibula slows the rate of union, it prevents malalignment.

Keywords: Tibia shaft fracture, intramedullary nailing, intact fibula, malunion, non-union

Tibial shaft fractures are the most frequently seen fractures of the long bones [1]. The fast pace of current lifestyles has led to an increasing incidence of motor vehicle accidents and sports accidents [2]. Conservative treatment can be applied in closed fractures with < 10mm shortness and < 5˚ angulation in any plane [3]. Surgical treatments are generally preferred to reduce complications (joint stiffness, non-union, malalignment) and provide an earlier return to work. Intramedullary nailing is the gold standard treatment method for tibial shaft fractures. As a minimally invasive and biological method, intramedullary nailing provides symmetrical and dynamic fracture fixation [4, 5].

Despite intramedullary nailing applied in tibial shaft fractures, non-union and malalignment may still be seen. In literature, non-union in tibial shaft fractures applied with intramedullary nailing has been reported

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as 5%-33%, and malalignment has been reportedas 16%, especially in distal fractures [6, 7].

One of the most important factors affecting non-union and malalignment is the status of the fibula. An intact fibula in tibial shaft fractures, especially in patients aged > 20 years, has been shown to increase the incidence of delayed union and non-union in the tibia [8]. To the best of our knowledge, there has been no previous study that has directly investigated the effect of the fibula being intact or fixed on tibial union and alignment in tibial fractures applied with intramedullary nailing.

The aim of this study was to investigate the effect of an intact or fixed fibula on tibial bone union and alignment in tibial shaft fractures treated with intramedullary nailing.

METHODS

A retrospective examination was made of 67 patients aged 19-85 years who were applied with intramedullary nailing for a tibial shaft fracture (AO-42) in our clinic between January 2010 and December 2016 (Fig. 1). All the fractures are caused by torsional injury resulted from low energy trauma. In AO classification diaphysis or shaft is located between proximal and distal end segment which is defined as the same length as the widest part of the epiphysis/metaphysis of the bone. Patients were included if they have isolated trauma resulting in tibial shaft fracture with or without fibula fracture. Patients were excluded if they had an open fracture or severe sort tissue injury (n = 2), multiple trauma (n = 2) or if data were not available (n = 19). Group 1 comprised 12 patients with anatomic fibula (intact or fixated if fractured) and tibial shaft fracture, and Group 2 comprised 32 patients with tibial shaft fracture and fibula that is not fixated. These 2 groups were evaluated with the Radiographic Union Scale in Tibial Fractures (RUST) score at 3 weeks, 3 months and 6 months, and in respect of alignment seen on anteroposterior and lateral radiographs taken on postoperative Day 1, at 6 weeks, 3 and 6 months. Patients not showing bone union at 6 months were followed up until union. Bone union can be evaluated with the RUST scoring system. RUST scoring is a radiographic evaluation method with high repeatability and reliability, which is used for tibial shaft fractures applied with intramedullary nailing. A RUST score ≥ 9 was accepted as union [9]. Malalignment was accepted as angulation > 5˚ on anteroposterior and/or lateral radiographs.

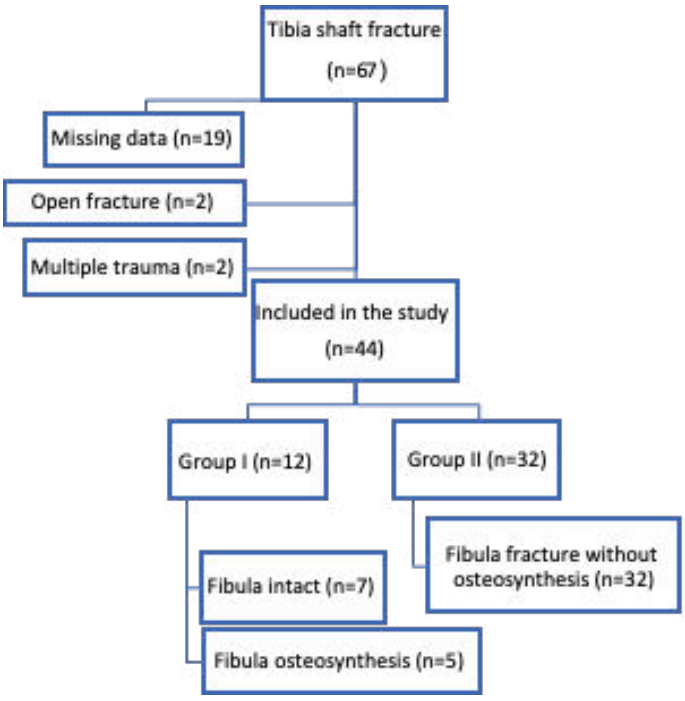

Fig. 1. Follow-up diagram.

Surgical Technique

Soft tissue was carefully evaluated preoperatively. Each patient was positioned supine on a radiolucent operating table. The C-arm was adjusted to come from the opposite side. Entry was made with an anterior approach to the knee. The tibial plateau was reached by separating the patellar tendon from the centre After closed reduction of the fracture with traction or with a weber clamp percutaneously, a locking, grooved antegrade tibia nail was applied. In patients with a fibula fracture in the distal quarter, which is a part of ankle joint, anatomic fixation of the fibula was applied for ankle stability. Very close follow-up was maintained in the first 24 hours, in respect of compartment syndrome.

Follow-Up

Postoperatively, patients who did not have a distal quarter fibula fracture were permitted weight-bearing

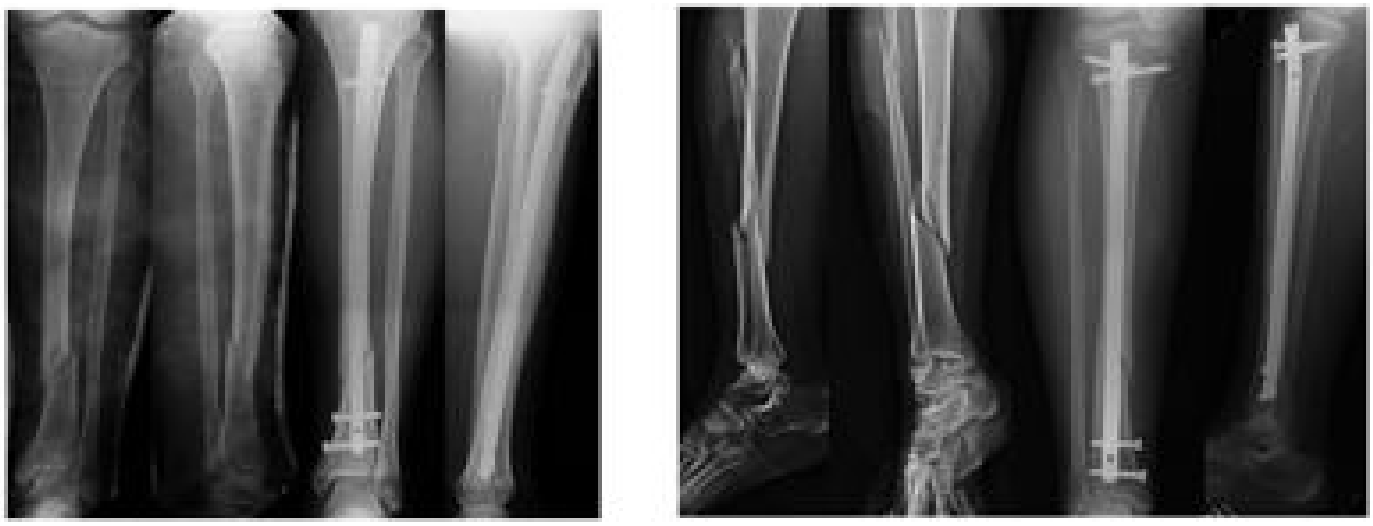

Fig. 2. Cases of intact and fixated fibula (preoperative and postoperative 6th month x-rays).

as tolerated. Patients with a distal fibula fracture were permitted weight-bearing after the 6th week postoperatively. All patients were given DVT prophylaxis and ankle and knee exercises were started in the early postoperative period. Until full bone union was obtained all patients attended regular follow-up examinations. Examples of cases from both groups are shown in Fig. 2.

Statistical Analysis

Data obtained in the study were analysed statistically using SPSS vn 13 (USA) software. Conformity of parametric values to normal distribution was assessed with the Shapiro Wilk test. Non-parametric variables were evaluated with the Mann Whitney U-test or the Fisher test. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

The patients comprised 24 males and 20 females (M/F:6/5) with a mean age of 42.7 years (range, 19-76 years). The demographic data of the groups are shown in Table 1. When patients were separated into 2 groups as those aged < 60 years and > 60 years, there was no significant difference in respect of the RUST scores at 6 weeks, 3 months and 6 months ($p > 0.05$). No significant difference was determined between the genders in respect of the RUST scores at 6 weeks, 3 months and 6 months ($p > 0.05$).

In Group 1, the mean RUST score was 5.16 at 6 weeks, 7.41 at 3 months, and 9.25 at 6 months. In Group 2, the mean RUST score was 6.59 at 6 weeks, 8.28 at 3 months, and 9.90 at 6 months. The differences at all 3 time points were determined to be statistically significant ($p = 0.040$). The time to union was determined as mean 20.8 weeks in Group 1 and mean 15.3 weeks in Group 2 ($p = 0.021$).

Non-union was observed in 3/12 (25%)patients in Group 1, and in 2/32 (6.3%) patients in Group 2 at 6 months. The total rate of non-union was 11% (Table 2). Due to delayed union in the 6th month, dynamisation was applied to 2 patients, and bone marrow injection was administered to 2 patients. In the 12th month, non-union was observed in 1 (2.2%) patient with an isolated tibia fracture. Fibula osteotomy was performed on this patient and union was obtained.

In the 8 patients with malalignment, union was achieved in the 6th month in 3 (37.5%), and of the 36 patients with normal alignment, non-union was still present in 2 (5.6%) in the 6th month. The RUST scores at 6 weeks, 3 months and 6 months were observed to be lower in the patients with malalignment compared to those with normal alignment.

Malalignment was observed in 1/12 (8.3%) patients in Group 1 (procurvatum) and in 7/32 (21.8%) patients in Group 2, of which 3 (9.3%) were varus, and 4 (12.5%) were valgus. The rate of malalignment was significantly lower in Group 1 than in Group 2.

The fracture levels were examined in the cases of

Table 1. Demographic data of patients

	Group 1 n = 12	Group 2 n = 32	Total
Age, years, mean (range)	38.2 (19-72)	44.1 (23-76)	42.7(19-76)
Gender			
Male, n (%)	8 (66.6%)	16 (50%)	24
Female, n (%)	4 (33.3%)	16 (50%)	20
BMI, kg/m^2 mean (range)	27.6 (24-35)	26.8 (22-34)	27.4 (22-35)

BMI = Body mass index

Table 2. Comparison of patients follow up data

	Group 1 n = 12	Group 2 n = 32	% *p* value
Malaligment rate	1 (8.3%)	7 (21.8%)	18%
Nonunion rate of 6th month	3/12 (25%)	2/32 (6.2%)	11%
RUST score			
6th week	5.16	6.59	
3th month	7.41	8.28	**0.040**
6th month	9.25	9.90	
Union (weeks)	20.3	15.8	**0.021**
Nonunion in malaligment rate	1/1 (100%)	2/7 (30%)	

RUST = RadiographicUnion Scale in Tibial Fractures

malalignment. Of the 37 cases with fibula fracture, 10 were at the same level as the tibia fracture and 27 were at a different level. Fixation was applied to 4 (40%) of the fractures at the same level, and to 4 (15%) of the fractures at different levels.

DISCUSSION

The application of intramedullary nailing is accepted as the gold standard treatment in the majority of tibial shaft fractures [10, 11]. No consensus has yet been reached on how a tibial fracture with concomitant fibula fracture or intact fibula should be treated.

The most significant finding of the current study was that when the fibula is intact, union of the tibia fracture is delayed while malalignment is prevented.

Delayed union or non-union of tibial fractures is an important problem because of delayed return to work and treatment becoming complicated. In literature, non-union rates have been reported at 5%-33% despite intramedullary nailing [6].

An intact fibula can cause distraction in the fracture line during intramedullary nailing of tibial fractures. It has been reported that 5 mm distraction of the fracture line in tibial fractures can prolong union to 8-12 months [12]. Isolated tibial fractures have been examined in literature and it has been reported that union problems have been experienced [13, 14]. In a study by Court Brown *et al*. [6], 14 isolated tibial fractures were compared with cases of both bone fractures and a significant difference was determined in the time to union (16.7 weeks vs.15.6 weeks). Balaji *et al*. [15] found the time to union to be mean 19.7 weeks in 56 cases of isolated tibial fracture with intact fibula. In the current study, the mean time to union was

determined as 20.8 weeks in Group 1 and 15.3 weeks in Group 2 ($p = 0.021$). The anatomic fibula (intact or with anatomic fixation) was observed to have prolonged the time to union.

Although there is no time limit for non-union in tibial fractures, delayed union is said to be union occurring at 3-4 months and non-union is accepted as no union within 6-8 months [16]. In a study of 1,106 patients applied with intramedullary nailing, Court Brown *et al*. [17] reported the non-union rate to be 4.4%. In the current study, the non-union rates according to the 6-month RUST scores (RUST < 9) were determined to be 25% in Group 1 and 6.2% in Group 2. The difference between the groups was statistically significant ($p = 0.040$). The anatomic fibula was observed to have delayed union of the tibial fracture. At 12 months postoperatively, non-union was observed in 1 (2.2%) patient and revision surgery was performed in this case.

Malalignment is often seen in distal tibial fractures. Zelle *et al*. [7]examined 1,125 patients and observed 16% malunion in intramedullary nailing applications. De Giacomo *et al*. [18] reported that modern methods of intramedullary nailing could lead to malunion. In the current study, malalignment was observed in 8 (18%) patients; 1 (8.3%) in Group 1 and 7 (21.8%) in Group 2. The anatomic fibula was found to have reduced malalignment.

In a study by De Giacomo *et al*. [18] of 122 patients with distal tibial fracture applied with intramedullary nailing, malalignment was observed most in patients with a fibula fracture at the same level as the tibial fracture. Similarly in the current study, malalignment was seen in 4 (40%) of the 10 patients with fractures at the same level and in 4 (15%) of the 27 patients with fractures at different levels.

Limitations

Limitations of the current study can be said to be the low number of patients and that the groups were not equal in number. In addition, other factors affecting union were not compared (smoking, socio-economic status, soft tissue status), clinical results and functional scores of the patients are not investigated and rotation of the tibia were not measured. There is a need for further, multi-centre, more extensive studies on this subject.

CONCLUSION

In conclusion, bone union of tibial fractures seems to be slower in patients with an anatomic fibula compared to those with a non-anatomic fibula. It is thought that the reason for this is that compression of the fracture is prevented by the fibula. Bone union in patients with malalignment is slower than in patients with normal alignment. Malalignment was seen less in patients with anatomic fibula compared to the patients with non-anatomic fibula. Age and gender were not determined to have any effect on bone union.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2020;6(4):343-346 Case Report

DOI: 10.18621/eurj.719715 Emergency Medicine

COVID-19 and stroke: a case report

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ABSTRACT

COVID-19 disease is a worldwide pandemic. Patients present to hospitals with upper and lower respiratory tract symptoms such as cough, fever, shortness of breath, however it can also be encountered with many different clinics. We aimed to share the patient who has COVID-19 and presented with stroke. A 67-year-old female patient presented to the emergency service complaints of mental fog and shortness of breath. She had known lung cancer, hypertension and diabetes. There were no signs compatible with COVID-19 in her history or examination. No feature was detected in her blood tests. Diffuse cerebral infarction was observed in diffusion MRI examination. The patient, whose general condition was poor, was taken into follow up in intensive care unit. On the eighth day of her follow-up, the patient passed away. In places where COVID-19 disease is observed commonly, it would be appropriate for emergency physicians to take COVID-19 disease into consideration in stroke cases.

Keywords: COVID-19, stroke, pandemic

COVID-19 disease is a worldwide pandemic. While most cases overcome the disease with mild symptoms, disease progresses much more severe in some cases. Patients present to hospitals with upper and lower respiratory tract symptoms such as cough, fever, shortness of breath, however it can also be encountered with many different clinics. We aimed to share the patient who has COVID-19 and presented to our emergency department with stroke.

CASE PRESENTATION

A 67-year-old female patient was tried to be woken up for breakfast in the morning of 23/03/2020 by her son, however she was brought to our emergency service by ambulance when it was noticed that she had mental fog and limited motion. She had known history of lung cancer, hypertension, and diabetes. She last had chemical treatment on 18/03/2020. On 23/03/2020, she presented to the emergency service of Sakarya University Training and Research Hospital with complaints of mental fog and shortness of breath. Blood pressure was 160/90 mmHg, pulse was 82 beats per min, respiratory rate was 26, fever was 36.8°C, oxygen saturation was 92 in room air and 98 with oxygen, and blood sugar was 82 mg/dL. Her electrocardiogram showed normal sinus rhythm. Her general condition was poor, her consciousness had tendency for sleep, there was no co-operation, and she responded to painful stimuli with a grimace. Pupillary was isochoric, light reflex was bilateral +/+, four extremities were partially mobile. According to the information received from her family, until the evening of 22/03/2020, she ran her errands, she could eat on her own, go to the toilet on her own, had normal

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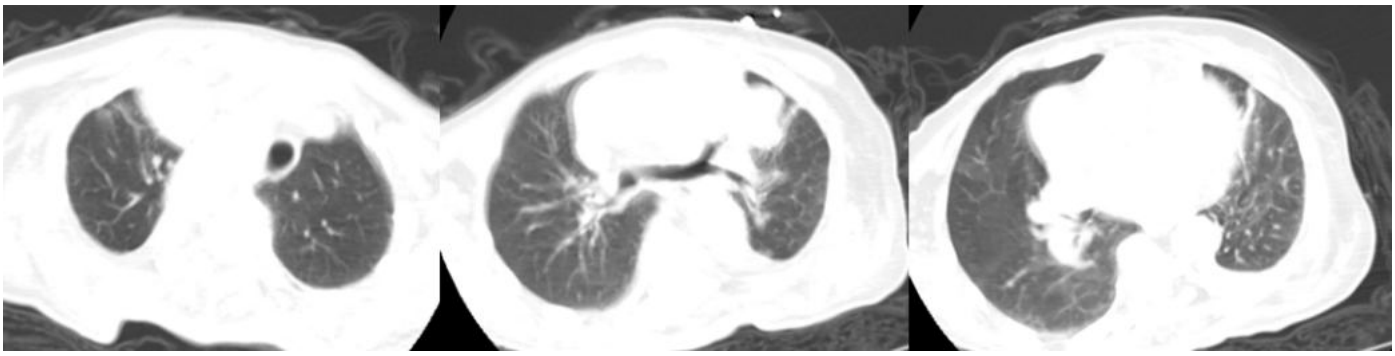

Fig. 1. **Thorax computed tomographic imaging**

speech and she had a history of suspected cranial metastasis.

Hemogram results showed hemoglobin as 10.8 g/dL, platelet as 140 K/µL and lymphocyte as 1.81 K/µL. Among the biochemistry parameters, CK-MB was measured as 27.5 U/L, urea as 46 mg/dL, and high sensitive Troponin I (hsTnI) as 429.1 ng/L. In blood gases, lactate was found as 0.6 mmol/L, pH as 7.349 and pCO_2 as 33.8 mmHg.

Brain and thorax non-contrasted computed tomography was performed to detect central pathologies especially and since she had shortness of breath. Brain tomography revealed low-density hyperdense areas in the left frontoparietal lobe, and cortical and subcortical hypodense areas in the right occipital lobe. The patient was consulted in the neurology department urgently and it was decided to perform cranial diffusion MRI to better distinguish between infarction and brain metastasis. Thorax tomography images of 23/03/2020 are shown in Fig. 1, and cranial diffusion MRI images of the same date are shown in Fig 2.

It was decided that the patient should be followed

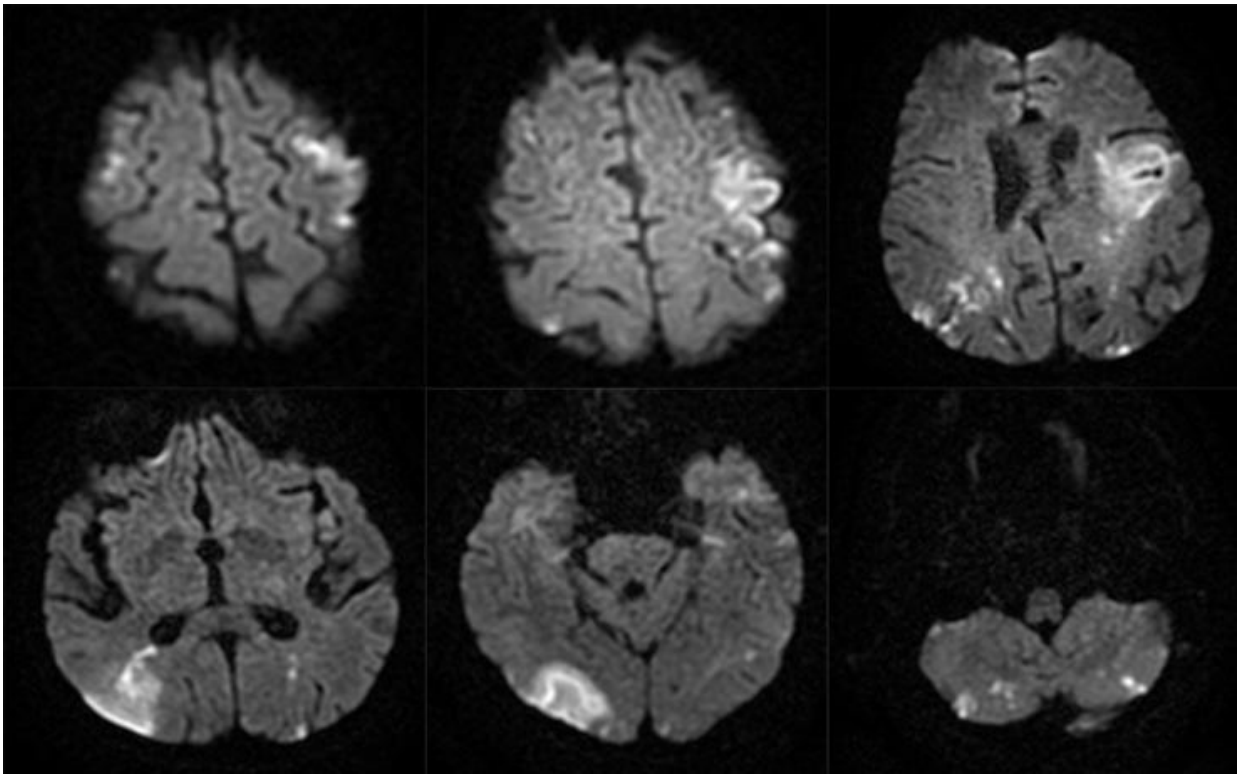

Fig. 2. **Cranial diffusion magnetic resonance imaging**

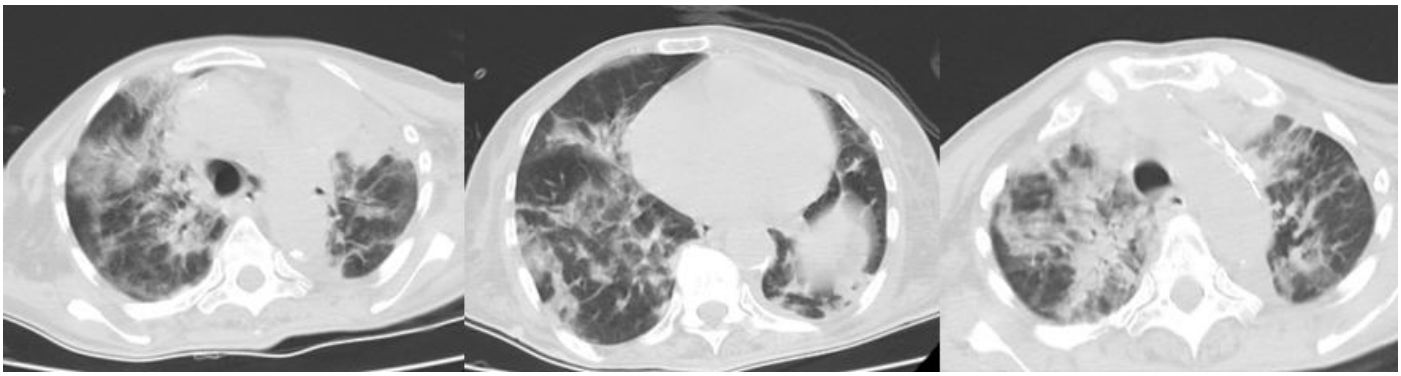

Fig. 3. Thorax computed tomographic imaging

up in intensive care unit since she had extensive cranial infarctions and due to her general condition. PCR sample of the patient was sent on 29/03/2020, after the patient's husband was taken under treatment in the hospital due to his positive COVID-19 PCR test and her thorax tomography was repeated. Significant changes were observed in the performed thorax tomography compared to the previous one. Images of thorax tomography of 29/03/2020 are shown in Fig. 3. Examinations in intensive care unit on 29/03/2020 showed Ferritin as > 2000 µg/L, D-dimer as 816 µg/L FEU, fibrinogen as 493 mg/dL, platelet as 107 K/µL, hemoglobin as 11 g/dL and lymphocyte as 0.253 K/uL. No significant change was observed in lactate, CO_2 or pH. The patient who had positive PCR test passed away in intensive care unit on 31.03.2020.

DISCUSSION

In patients presenting to the emergency department with stroke findings may have COVID-19 disease. It was reported that COVID-19 disease was detected in one patient presenting with only weakness of the right extremity [1]. The reason for this may be microtrombus caused by COVID-19 disease. Especially, severe COVID-19 patients may face the risk of both thrombosis and hemorrhage [2]. COVID-19 disease was severe in 60% of patients with high D-dimer level [3]. When patients who died from COVID-19 and who survived were compared, high level of D-dimer supports this [4]. Our patient's D-dimer level was also high and supports these results.

Ferritin level also started to emerge as an important finding in COVID-19 patients. It can be observed that ferritin level rises to the values expressed in thousands [5]. High ferritin levels in COVID-19 patients are associated with death [6]. Our patient's ferritin being > 2000 µg/L corresponds to this result.

The presence of lymphopenia in patients is considered as a severe disease factor for COVID-19 [7]. Although our patient did not have lymphopenia, on 23/03/2020, when she first presented to the emergency service, she developed lymphopenia during her hospital stay. During the six-day period, lymphocyte count of our patient decreased from 1.81 K/uL to 0.25 K/uL.

There are publications stating that the COVID-19 patients with critical conditions have increased fibrinogen levels [4, 8]. Fibrinogen count of our patient was 493 mg/dL and was higher than normal.

Hypercoagulability is one of the tables that is encountered in cancer patients [9]. The fact that our patient had a history of lung cancer and also was diagnosed with COVID-19 may strengthen the possibility of hypercoagulability and cause thrombosis-related stroke. Our patient was also a diabetes patient. Diabetes disease has been reported to adversely affect the prognosis of COVID-19 [10]. It is also frequently reported that higher mortality is observed in elderly COVID-19 patients with hypertension [11]. Our patient had hypertension and therefore being under treatment may also be a factor in poor prognosis course. This case may give us an idea that when the number of comorbid conditions increase, mortality ratio may increase.

CONCLUSION

COVID-19 disease progresses with symptoms

especially such as cough, fever and shortness of breath. Most patients overcome the disease with mild symptoms. However, it should be taken into consideration that COVID-19 disease may cause a more severe clinical table and may be encountered as a stroke case, except for symptoms such as cough and fever. In places where COVID-19 disease is observed commonly, it would be appropriate for emergency physicians to take COVID-19 disease into consideration in stroke cases.

Informed consent

Written informed consent was obtained from the patient's family for publication of this case and any accompanying images.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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The European Research Journal 2020;6(4):347-350 Case Report

DOI: 10.18621/eurj.690722 *Cardiovascular Surgery*

The treatment of coronary artery aneurysm with a hybrid approach

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ABSTRACT

Objectives: Coronary artery aneurysms (CAAs) are rare cases that generally present with ischemic symptoms. Although coronary artery bypass surgery is widely performed in treatment, endovascular procedures have also begun being used in recent years. We describe a patient developing acute myocardial infarction due to CAA at a young age, despite the absence of any risk factor, followed by rapidly growing aneurysm. This patient was treated with a hybrid approach, very rare case in the literature.

Keywords: Coronary artery aneurysm, hybrid treatment, coil embolization, coronary artery bypass surgery

Coronary artery aneurysms (CAA) are reported incidence of 0.02-5.2% [1-4]. The most common etiological cause is atherosclerosis. Other causes are congenital factors, inflammation, connective tissue diseases, drug use, or procedural trauma [1, 2]. Ischemic complications associated with thrombus and distal embolization are frequently observed in aneurysms. However, rupture is the most feared complication.

CAAs are generally treated surgically. However, endovascular procedures have also begun being used in recent years. Another option is medical treatment. However, a hybrid method consisting of surgery and endovascular procedures has not to date been used to treat this disease. We report the first case of CAA treated using a hybrid method. No risk factors were present in this young patient.

CASE PRESENTATION

An 18-year-old male patient presented due to chest pain. In coronary angiography, the proximal left anterior descending artery (LAD) was completely obstructed. Emergency percutaneous coronary intervention was attempted, but was unsuccessful. The patient was transferred to the coronary intensive care unit. It was planned to perform interventional treatment for total occlusion lesions at another session. After which patency was achieved in the LAD. Aneurysmatic dilation, 2.5 cm in diameter was observed in the proximal LAD, and stenosis was present after dilation (Fig. 1). A stent was implanted in the LAD. Two and a half months subsequently, the patient again presented with chest pain. Control angiography revealed that the 2.5 cm aneurysm had grown to 4.5 cm (Fig. 2), and the patient was referred for surgery. The presence of connective tissue disease was investigated, but no pathology was determined. There was no risk factor for atherosclerosis.

the aneurysm was very close to the bifurcation, we decided to adopt a hybrid approach in order to reduce the surgical risk. We decided to close the aneurysm using coils before performing coronary

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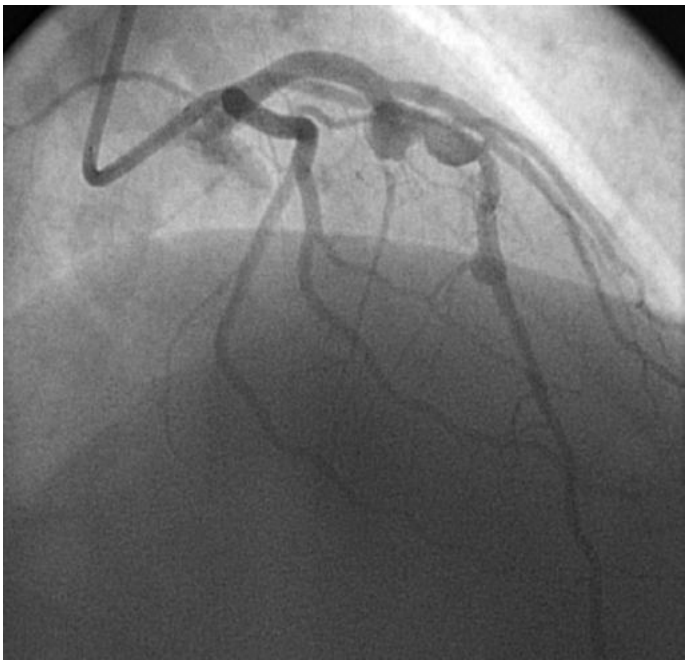

Fig. 1. First angiography showed multiple coronary aneurysms in LAD artery.

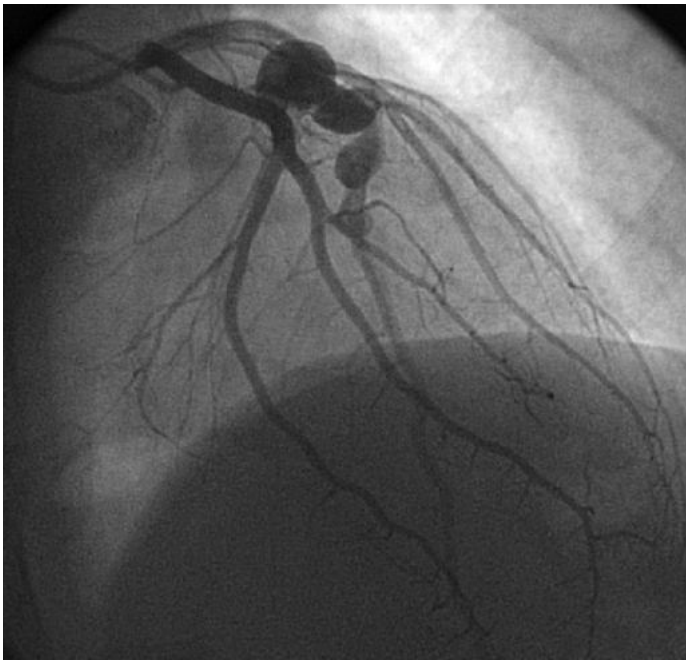

Fig. 2. After 2.5 months, control angiography showed enlargement of coronary artery aneurysms.

bypass. The proximal part of the aneurysm was first closed with a 4 mm × 100 mm coil (Blockade Medical, Irvine, California, USA). However, the flow was not completely interrupted. A second 4 mm × 100 mm coil was inserted into the aneurysm, and no flow was observed at fluoroscopy. Cardiopulmonary bypass was established. The aneurysm in the LAD was visualized following medial displacement of the heart (Fig. 3). Cardiac arrest was established with a cross-clamp to the aorta. The aneurysm sac was ligated from the distal part, and coronary artery bypass grafting was then performed on the LAD artery using the left anterior thoracic artery (LITA).

No problems developed in the postoperative period, and the patient remained in the ICU for one day. He was discharged on the fifth day postoperatively. Control coronary angiography was performed one month later. The LITA-LAD

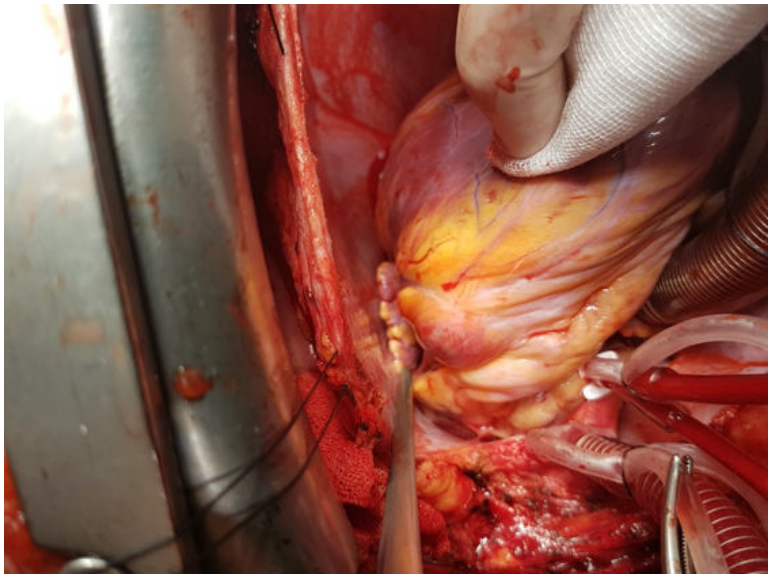

Fig. 3. Operative view of coronary artery aneurysm.

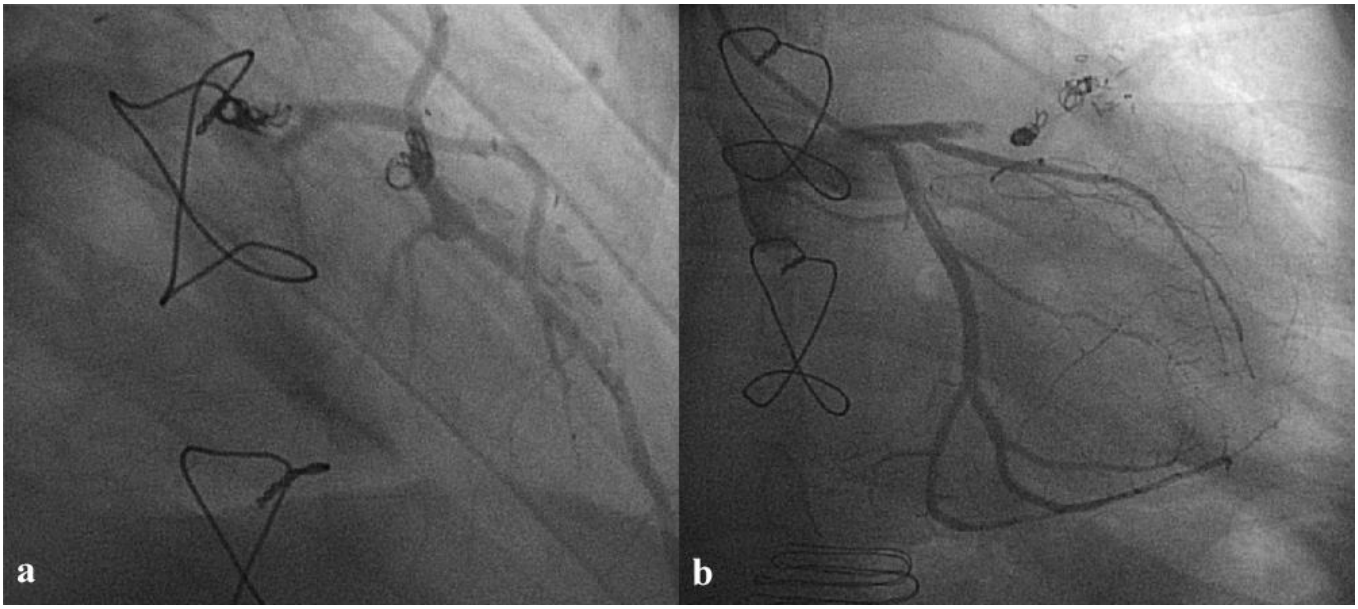

Fig. 4. Postoperative coronary angiography. (a) Patent LITA-LAD anastomosis and (b) the aneurysm sac could not be visualized.

anastomosis was patent (Fig. 4a) and the aneurysm sac could not be visualized (Fig. 4b).

DISCUSSION

Thrombotic complications are seen in more than 75% of CAAs [2, 3, 5]. Our patient also presented to hospital due to myocardial infarction. However, another fatal complication of CAAs is rupture. As in our case, rupture is inevitable if an aneurysm doubles in size in two months.

There is no consensus regarding the treatment of CAAs. Therapeutic options include surgery, percutaneous interventions, and medical treatment. Keyser *et al*. [3] stated that three out of five cases of aneurysms exceeding 5 cm in size died under conservative therapy. Surgery is the most common method in the treatment of CAAs. The most common operative technique is conventional coronary bypass surgery with ligation of the aneurysm. Other surgical methods include aneurysm resection and interposition graft, aneurysmorrhaphy, or patch plasty.

Endovascular therapy with stent-grafts has also been reported in CAA treatment in recent years. However, these grafts have high rates of stenosis and obstruction [1]. Surgery is therefore still regarded as the best option. The simplest technique in operative therapy is coronary artery bypass grafting with ligation of the distal and proximal aneurysm sac. However, if the aneurysm is very close to the left main artery, as in our case, ligating the proximal sac involves a risk of complication. Closing the proximal part with endovascular methods will be a good method in order to avoid complication. We therefore closed the beginning of the aneurysm using a coil, and surgery consisted of a simple, single coronary artery bypass operation. We know of no other case of CAA being treated with this method.

CONCLUSION

In conclusion, although there is still no consensus on the optimal treatment of CAAs, hybrid methods are an easy and safe option.

Informed consent

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

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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The European Research Journal 2020;6(4):351-353 Case Report

DOI: 10.18621/eurj.601306 *Cardiovascular Surgery*

Lower limb deep venous thrombosis due to vertebral osteophyte: a May-Thurner-like syndrome

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ABSTRACT

Lower extremity venous thrombosis is a risky condition that may cause crucial complications including pulmonary embolism and post-thrombotic syndrome. May-Thurner syndrome is a venous compression syndrome resulting in compression of the left common iliac vein by the overriding right iliac artery. In this case, left common iliac vein compression arises from the vertebral osteophyte.

Keywords: Vertebral osteophyte, May-Thurner syndrome, venous thrombosis, Cockett syndrome

May-Thurner Syndrome (MTS) was first observed in 1851 by Virchow as the anatomical variation of the left common iliac vein. However, the pathophysiological description of this disease was made by May-Thurner in 1956. This disease in which the left common iliac vein is exposed to external compression is also known as iliac venous compression syndrome, Iliocaval compression syndrome and Cockett syndrome [1]. Depending on this compression situation, the risk of lower extremity deep venous thrombosis (DVT) is increasing.

DVT is a serious condition that may lead to fatal complications like pulmonary embolism; therefore, it should be treated as soon as it is diagnosed. The etiology of DVT is explained by the Virchow triad. These are stasis in blood flow, vessel wall and coagulation disorders. The most serious complication of DVT which is almost the same frequency in both genders is the pulmonary embolism. Although the frequency of DVT is 1/1000 in the general population, its frequency is increasing in the elderly, and immobile population [2]. Early diagnosis of the disease and its treatment strategy are extremely important.

CASE PRESENTATION

A 61-year-old man was admitted to our emergency department with complaints of pain and swelling in the left lower extremity. Venous doppler ultrasonography revealed acute thrombosis in the popliteal and femoral veins. His medical history did not contain any risk factors like immobilization, malignancy or a systemic disease. Accordingly, we performed computed tomographic angiography (CTA) to exhibit the etiology of the venous thrombosis. CTA showed a vertebral osteophyte that caused compression of the left common iliac vein (Fig.1.A-D). The patient was hospitalized and received low molecular weight heparin therapy with warfarin. He was discharged one week later when international normalized ratio (INR) was effective value (INR: 2.5-

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3).Patient did not have any complaints during 1-year follow-up and INR values were within normal range for the patients.

DISCUSSION

MTS is a venous compression syndrome resulting in compression of the left common iliac vein by the overriding right iliac artery. The causes of ilocaval compression syndrome include; iliac venous thrombosis, arterial compression-related web (May-Thurner), previous DVT-related scar, pelvic cancer / abscess, fibroids / fibroids resulting with uterine hypertrophy, pregnancy, aorta-iliac aneurysms, postoperative hematome and vertebral osteophytes [3]. Doppler ultrasonography (DUSG) is the first option in diagnosis. The DUSG, which is used as the most common diagnostic tool, may cause the possible misdiagnosis of iliocaval compression when no further tests are performed. In clinical suspicious cases, CT angiography and venography should be used as a diagnostic method. In particular, the underlying iliocaval compression syndromes should be considered in repeated left lower extremity DVTs. That left lower extremity DVTs are 3-8 times higher than that of right side can be explained by compression syndromes. In a rare case of situs inversus totalis, MTS may be presented with the right lower extremity DVT clinic [4]. In the physical examination and clinical condition of the patient, this detail should not be overlooked.

The most common treatment for DVT is to start warfarin therapy with low molecular weight heparin and to provide effective INR range. The duration of treatment is six months for patients with the first DVT whose underlying causes are unknown. In patients with recurrent DVT, pulmonary embolism, or blood diseases, treatment may continue for life. New anticoagulant treatment options have been replaced in recent years [5]. The advantage of these treatment options is not requiring INR follow-up.

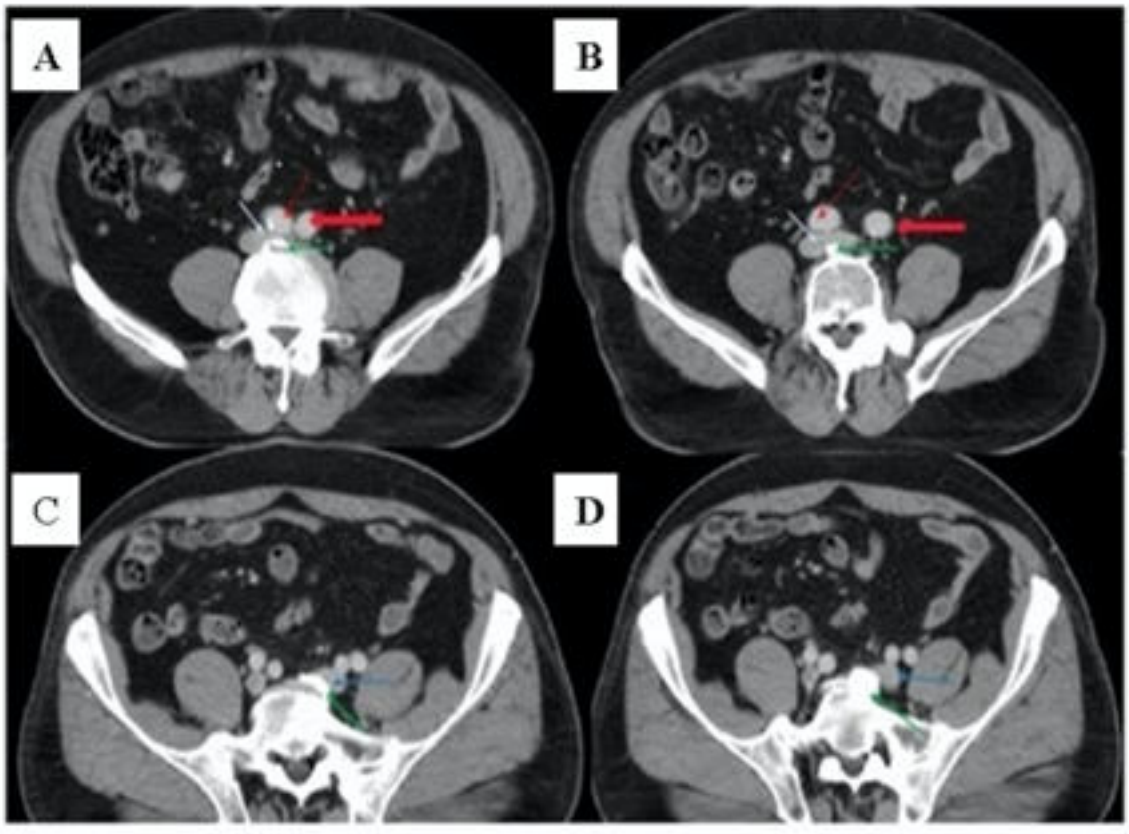

Fig. 1. (A, B, C, D) Computed tomographic angiographic images of compressing common iliac vein by the vertebral osteophyte (**Yellow arrow:** vertebral osteophte, **Light blue arrow:** vena cava inferior bifurcation, Blue arrow: left common iliac vein, **Thick red arrow:** left common iliac artery, **Thin red arrow:** right common iliac artery).

Recently, endovascular treatment options such as mechanical thrombectomy have been included in addition to the medical treatment. That patients with MTS have symptoms is a requirement for treatment. Le *et al*. [6] had 111 MTS patients underwent endovascular treatment. Patients undergoing thrombectomy were treated with stents to eliminate pressure. After the operation, these patients were followed for six months with warfarin or rivaroxaban (Xarelto, Bayer Pharma AG, Berlin, Germany) [6]. However, patient with vertebral osteopathy wasn't observed in this large group of patients.

When we evaluated our case, the iliac compression of our patient was due to vertebral osteophytes which was a rare condition. For our patient, no endovascular treatment was planned against possible damage to the vessel due to osteophyte. In addition, his symptoms regressed under medical follow-up. Surgical treatment options such as venous bypass may be considered in patients with recurrent DVT and pulmonary embolism whose symptoms do not regress.

CONCLUSION

In conclusion, the treatment of the patient with vertebral osteophyte, which is a rare cause of ilioocaval compression syndrome, can be provided with medical treatment. Surgery can be considered in untreated patients.

Informed consent

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

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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The European Research Journal 2020;6(4):354-358 Case Report

DOI: 10.18621/eurj.594013 *Medical Oncology*

Recurrence of appendix tumor: case report and literature update

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ABSTRACT

Herein, we report a case of appendix adenocarcinoma who presented with a recurrence 8 years after the initial diagnosis. A 54-year-old male underwent appendectomy in 2009. The pathology revealed a 1.7 cm diameter low grade mucinous carcinoid tumor. Any additional treatment was not recommended for patient other than appendectomy. The patient was admitted with the symptoms of ileus at 8 years after surgery and then underwent to right hemicolectomy in 2017. On histopathological examination of the specimen revealed a Goblet cell adenocarcinoid tumor, arising from iliocecal valv with pericolorectal tissue invasion of 5 cm in diameter. Lymph-node metastases were found in 16 dissected lymph nodes. The patient was initiated to treat with combined capecitabine and oxaliplatin chemotherapy. There is no clear evidence to support the superiority of any particular chemotherapy regimen for adjuvant treatment of appendix tumors. In this regard more studies are needed to use combined regimens.

Keywords: Appendiceal, adenocarcinoma, chemotherapy

Appendiceal tumors are rare tumors which are detected in approximately 1% of appendectomy specimens and they account for only 0.5% of all intestinal tumors. Neuroendocrine tumors (NET) are the most common tumors of the appendix, comprising more than 50% of all appendix tumours in majority of the series [1]. Clinical behavior and prognosis of appendix tumours are associated with the tumor size. The risk of metastasis in tumors less than 2cm (approximately 95% of tumors) is reported to be low. It may be suggested that approximately one third of larger lesions are metastatic at diagnosis, and this metastases are usually limited to regional lymph nodes [2].

Appendix tumors that share the histological characteristics of both carcinoids and adenocarcinomas are defined as Goblet cell carcinomas (GCC) (adenocarcinoids). The prognosis of GCC are poorer than the carcinoids however better than the adenocarcinomas. GCC frequently present with acute or chronic abdominal pain but small part of cases are diagnosed incidentally after appendectomy. The reported 5-year survival rate of GCC is approximately 78% for all stages [3].

In contrast to other appendix tumors, appendix adenocarcinomas more often present with the signs and symptoms of acute appendicitis. Other clinical manifestations include the palpable abdominal mass, abdominal pain and ascites. Appendix adenocarcinoma is incidentally found during surgery in 20% of

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the cases [4]. We present a case who was operated due to the recurrence of appendix GCC 8 years after the initial diagnosis.

CASE PRESENTATION

A 54-year-old male patient underwent appendectomy for acute appendicitis in 2009. The pathology revealed a 1.7 cm diameter low grade mucinous carcinoid tumor in the appendix that infiltrated all muscular layers. The radial surgical border was interpreted as closer than 0.1 cm and no subserosal, lymphovascular or perineural invasion was detected. Immunohistochemistry revealed that the tumor cells were positive for Ki-67=2. At the same time the indium-111 octreotide scintigraphy and contrasted computed tomography (CT) scan was performed. The patient who did not have evidence of residual lesion or distant metastasis by imaging tests,

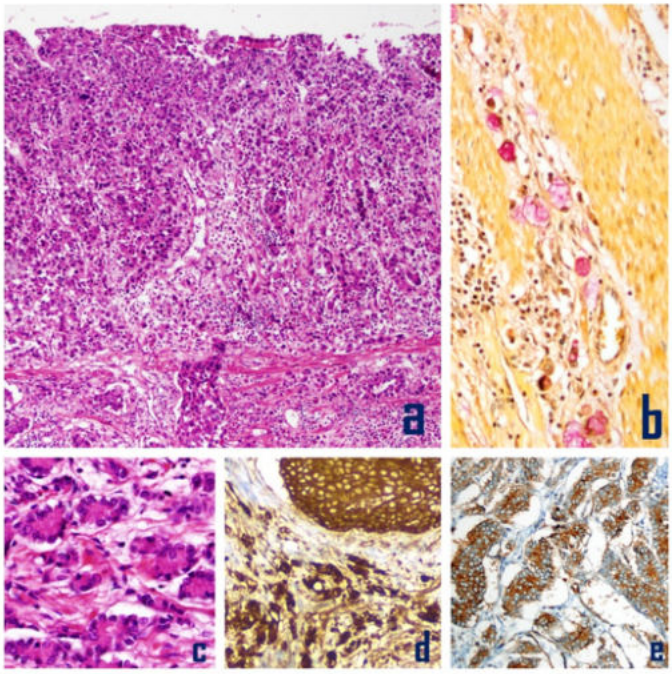

Fig. 1. Intestinal tissue. a) umoral tissue with throughout all layers infiltration and extensive lymphovascular invasion, HE×40; b) Immunohistochemistry studies showed the infiltrative signet-ring cells in muscle tissue stained positive for mucicarmine, ×200; c) Tumor cells with fine nuclear chromatin pattern, HE×400; d) Tumor cells with diffuse positive immunohistochemical staining of MOC-31, ×100; and e) Diffuse immunohistochemical stainingof synaptophisin intumor cells, ×200.

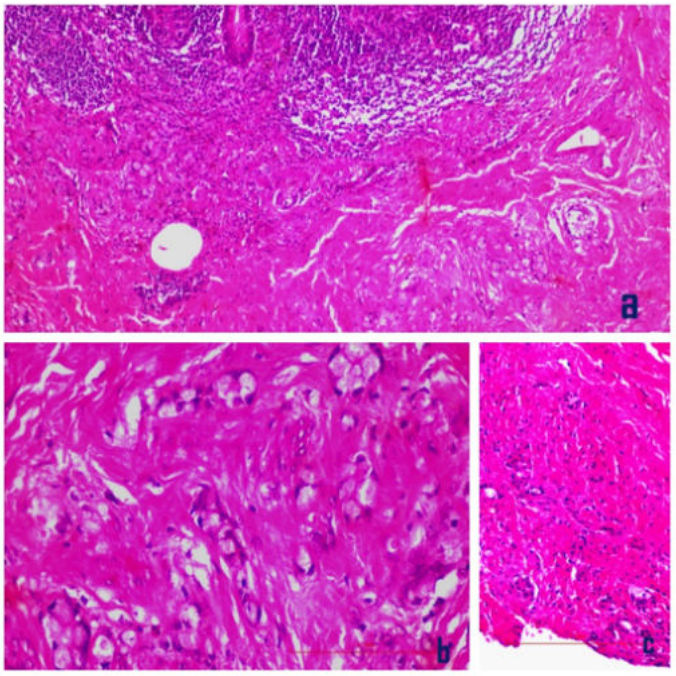

Fig. 2. Appendix tissue. a) Infiltrative tumor cells in mucosa and muscle tissue, HE×40; b) Tumor tissue of Goblet cells in small groups, HE×400; and c) Tumor cell islands that infiltrating the subserosal layer, HE×200.

so we was not recommended any additional treatment other than appendectomy. The patient who has not come for follow up visits during 8 years after discharge from the hospital, was applied to the emergency department with the symptoms of ileus in 2017 and then right hemicolectomy was performed at the Department of Surgery. On histopathological examination of the specimen revealed a GCC, arising from iliocecal valv with pericolorectal tissue invasion of 5 cm in diameter. Lymph-node metastases were found in 16 out of 18 dissected lymph nodes. The pathological findings demonstrated that perineural invasion was positive, extensive lymphovascular invasion was positive, surgical borders were negative. Immunohistochemistry revealed that the tumor cells were positive for Ki-67=38, synaptophysin CEA and MOC31 and negative for chromogranin and CD56 (Fig. 1).

After histopathological assessment of both previous and present specimens, the patient was diagnosed with appendix recurrent GCC (Fig. 2). A CT and Galium 68-positron emission tomography did not show distant metastasis. The chromogranin level of 29.9 (< 94) was regarded normal. Adjuvant chemotherapy was initiated 8 weeks after surgery with

combined capecitabine and oxaliplatin chemotherapy. Patient recieved oxaliplatin 130 mg/m2 i.v on day 1 and capecitabine 1250 mg/m2 orally twice daily on days 1 to 14. This regimen was administered every 21 days for six months. However, peritoneal metastasis was detected at 8 months post-adjuvant chemotherapy. First-line irinotecan-based chemotherapy was offered as a treatment option. The full informed consent was given and then the treatment was started.

DISCUSSION

The appendix NETs are diagnosed at a younger age than the other appendix tumors with an average age of 40 years. The incidence is more frequent in women. The majority of NETs are located at the distal 1/3 of the appendix, where the likelihood of obstruction is lower. There has been much controversy the optimal surgical treatment of patients with appendix NETs. Since, the most of cases are usually discovered incidentally during appendectomy it is necessary to decide whether a right colectomy is performed. Evidence based indications for the right hemicolectomy is limited in patients with an appendix NETs [1].

In the Mayo Clinic case series of 150 patients with appendiceal NET was observed no metastasis in 127 patients with tumors sized less than 2 cm, however metastasis were detected 3 out of 14 patients with tumors sized 2-3 cm, and 4 out of 9 patients with tumors sized greater than 4 cm [2]. In single center review study of appendix NETs also reported that the risk of lymph node metastasis in patients with tumors size < 1.0 cm, 1-1.9 cm and > 2 cm indiameter was were 0, 7.5 and 33, respectively [5]. These data indicate that tumor size is an important determinant of surgical strategies.

The North American Neuroendocrine Tumor Society (NANETS) and European Neuroendocrine Tumor Society (ENETS) recommend a hemicolectomy for tumors greater than 2 cm or for tumors sized between 1 and 2 cm in the presence of lymphovascular invasion, deep mesoappendiceal invasion, positive or unclear margins, higher proliferation rate (grade 2) or mixed histology [6, 7].

In our case, the first surgical pathology was evaluated as mucinous NET. Since the tumor size was 1.7 cm and there was no lymphovascular invasion, right hemicolectomy was not recommended at that time. However, right hemicolectomy could have been performed due to the presence of muscular layer invasion and 0.1 cm surgical margin. Follow-up was recommended to the patient after appendectomy.

The recommendation of follow-up is based on the tumor size. For appendix NET that are less than 2 cm and localized to the appendix, no further routine follow-up is required after surgery and tests should be performed only in the presence of symptoms. For tumors larger than 2 cm, evaluation including history, physical examination, tumor markers (5-hydroxy indoleacetic acid, chromogranin) and abdominal imaging is performed between 3-12 months after resection. It is recommended to follow-up with anamnesis, physical examination, and tumor markers every 6 to 12 months after the first year. Imaging tests after the first year is suggested only if clinically indicated [7]. Our patient did not come for scheduled post-discharge outpatient follow-up appointments during 8 years.

Somatostatin receptors which are overexpressed in NETs, might be detected by using imaging techniques. In symptomatic patients with metastatic tumor that have somatostatin receptor positive, somatostatin analogs can be beneficial in relieving the symptoms. Somatostatin analogues also prolong overall survival and prevent disease progression in asymptomatic patients. Everolimus is a treatment option for patients with disease progression after somatostatin analog therapy. Liver resection or if resection is impossible hepatic artery embolization may be considered to improve symptoms in selected patients. The optimal treatment modalities for the progressive metastatic gastrointestinal NET patients has not been established. Consequently, there is no standard therapy regimen for these patients and the role of chemotherapy is controversial [8].

The optimal treatment for appendix GCC is also unclear. Although there have been some reports recommend to treate by simple appendectomy alone in localized low-grade GCC of the appendix, in the literature suggests that a right hemicolectomy within 3 months after appendectomy if the patient is eligible for additional surgery. In adenocarcinomas, intraperitoneal spread is more common than GCC. Debulking of the abdominal tumor mass with

aggressive surgery is associated with improving overall survival as well as symptom control. The rate of response to chemotherapy might be higher in appendix GCC than appendix adenocarcinomas [3, 9]. The role of adjuvant therapy in early stage GCC is unknown. Although there is no data supporting the use of chemotherapy; if lymph node involvement is present, systemic chemotherapy is recommended as in adenocarcinomas [9]. In the literature, metastatic GCC patient with a complete remission was reported following FOLFOX chemotherapy (fluorouracil (FU), leucovorin and oxaliplatin) [10]. Our case was diagnosed as an Goblet cell carcinoid tumor (adenocarcinoid) GCC of the appendix after evaluating the present and previous pathology preparations together. In our patient, although there was no visible tumor after surgery, adjuvant capecitabine and oxaliplatin treatment was planned due to presence of extensive lymph node involvement and recurrence.

The appendix adenocarcinomas are divided into three different histological types which are classified as mucinous type, colonic type and signet-ring cell type adenocarcinomas, in order of frequency. Signet ring cell carcinomas of the appendix have a very poor prognosis [11]. Some retrospective series have shown that survival is better in appendix adenocarcinoma patients who underwent colectomy compared to appendectomy. Although optimal treatment for appendix adenocarcinomas is the right colectomy, some authors recommend appendectomy because of the low likelihood of lymph node metastasis in well differentiated lesions that invade no deeper than the submucosa and they suggest hemicolectomy for deeply invasive tumors [4].

The role of adjuvant chemotherapy for appendix adenocarcinomas is unknown. Though the lack of available data, many specialists recommend adjuvant fluorouracil-based chemotherapy for lymph node-positive patients. However, the specific benefit of this approach has not been proven [12]. The benefit of adjuvant radiotherapy is also uncertain and no randomized trials have been performed as in chemotherapy. In a small retrospective study, it has been suggested that postoperative radiotherapy in local advanced disease improves local control and survival. In the same study, although in 5 out of 10 patients had a local recurrence after surgery, among 5 patients receiving postoperative radiotherapy only 1 patient had a local recurrence [13].

A recurrence of appendix adenocarcinomas often presents as intraperitoneal spread. Therefore surgical treatment of intraabdominal disease and an aggressive approach including hyperthermic intraperitoneal chemotherapy (HIPEC) may be predicted to control peritoneal disease as in the treatment of pseudomixoma peritonei (PMP). However, different than the PMP, aggressive cytoreductive surgery and HIPEC are less likely to provide long-term benefit for mucinous peritoneal carcinomatosis, and patient selection is critical [14].

There is no systematic study indicating the benefit of systemic chemotherapy in metastatic appendix adenocarcinomas and PMP. In a study with 54 patients, majority of patients (84%) received capecitabine or FU. Clinical benefit was obtained in 30 (55%) patients with a median progression free survival of 7.6 months. A complete response in 2 patients, partial response in 11 (24%) patients, and stable disease in 17 (32%) patients was provided. The mean survival was detected as 55 months in that study [15].

CONCLUSION

There is no clear evidence to support the superiority of any particular chemotherapy regimen for adjuvant treatment of appendix tumors. The combinations of fluorouracil and irinotecan or oxaliplatin increase antitumor activity and efficacy compared with single agent fluorouracil in patients with metastatic colorectal adenocarcinomas. In conclusion, more studies are needed to use these combined regimens instead of single agent flurourasil in the adjuvant treatment of appendix GCC.

Informed consent

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

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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The European Research Journal 2020;6(4):359-361 Case Report

DOI: 10.18621/eurj.558457 *Physical Medicine and Rehabilitation*

Parsonage-Turner syndrome presenting with left shoulder pain and weakness: a case report

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ABSTRACT

Parsonage-Turner syndrome is a clinical syndrome that begins with a sudden, neuropathic pain on the shoulder girdle, followed by pain loss over time. It is a rare syndrome that can be overlooked during differential diagnosis of shoulder pain and weakness. In this paper, we aimed to present a 39-year-old male patient with sudden onset left shoulder pain and weakness who were diagnosed with Parsonage-Turner syndrome.
Keywords: Parsonage-Turner syndrome, shoulder pain, weakness

Parsonage-Turner syndrome (PTS) was first demonstrated by Parsonage and Turner in 1948. However, the syndrome has different names such as acute brachial neuropathy, acute brachial plexitis and idiopathic brachial plexopathy [1]. It is a clinical syndrome characterized by sudden onset, severe and mostly neuropathic chartershoulder pain and subsequently developing muscle weakness [2]. PTS frequently confused with shoulder and neck pathologies and the syndrome must be considered during the differential diagnosis of patients presenting with shoulder pain and weakness [3]. The frequency of PTS is known as 1.64/100,000 and more common in 20-60 age male population and is a treatable disease with good prognosis [2]. The aim of presenting this case report is to raise awareness of PTS and emphasize that it should be included in the differential diagnosis of shoulder pain and upper extremity weakness.

CASE PRESENTATION

A 39-year-old male patient was admitted to our outpatient clinic with complaints of pain and weaknessonhis left shoulder. A sudden onset of left shoulder pain occured one month ago and weakness of shoulder added to pain in the following few days. Patient complained of numbness of left hand at the same time and applied to orthopedics department with these complaints. The patient was diagnosed with muscle rupture and the necessary drugs were started but there was no improvement onhis complaints. There were no history of trauma, infection or neck painand he did not describe another systemic disease. When the patient was questioned neurologically, it was understood that there was no neurological problem in addition to the current situation. Physical examination showed atrophy of the left deltoid muscle. The range of motion of the upper left limb joints was normal. His elbow flexion was 2/5, extension 2/5, wrist dorsiflexion was 2/5 and finger movements were 5/5.Hypoesthesia was detected on the lateral side of the left arm and forearm. The left biceps-brachioradial and triceps reflexes were decreased and there was no pathological reflex. The other extremities and cranial system were normal. No pathology was found in the brain-cervical-brachial

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Fig. 1. 2/5 shoulder flexion muscle strength at the second week of rehabilitation program

Fig. 2. 5/5 shoulder flexion muscle strength at the end of the rehabilitation program.

plexus and shoulder magnetic resonance imagingand no pathology was found in the laboratory tests of the patient. In the electroneuromyography, the patient was found to have plexopathy in the subacute process in the upper-middle trunk of the brachial plexus. Chest X-ray required suspicion of possible lung diseases, doubtful consolidation was detected and the patient consultated to chest diseases. A thoracic computerized tomography (CT) scan was recommended and the result of CT was reported as normal. In the light of these findings, the patient was diagnosed as PTS and 40 mg methylprednisolone treatment withexercise program were initiated. After using methylprednisolone and 30 sessions of exercise program, the patient's pain and muscle strength improved andhe was discharged with full recovery (Figs. 1 and 2).

DISCUSSION

Shoulder pain is a significant part of the patients admitted to the physical medicine and rehabilitation outpatient clinic. Although there are many intrinsic and extrinsic causes of shoulder pain, the most common cause is known as subacromial impingement syndrome.In cases where shoulder pain is accompanied by weakness, brachial plexus, cervical roots, spinal cord and cranial system pathologies should be considered in the differential diagnosis.In this respect, PTS, which is a treatable disease with good prognosismay be seen as an important syndrome to be considered in the differential diagnosis of shoulder pain and weakness.The frequency of PTS is known as 1.64/100,000 and more common in 20-60 age range male population [2]. The most common cause of brachial plexopathies is known as trauma. However, PTS was pointed out asthe most common cause of brachial plexopathies in a study evaluating 203 cases [4]. There was no difference in terms of frequency of involvement between the right and left extremities and no correlation was found for the dominant hand. Involvement is usually unilateral but bilateral involvement may be seen as 1/3 ratio [5, 6]. The cause of PTS is not known yet. Although viral infections (influenza-B, parvovirus, HIV), vaccines, autoimmune causes, heavy exercise, previous operations and hereditary causes have been blamed, the etiology has not been elucidated [7-9]. Although there was no story of heavy exercise in our case, it was thought that the shoulder might beexposed to continuous microtrauma due to the profession of cookery. As in our case, laboratory tests(complete blood count, erythrocyte sedimentation rate, serum electrolytes, liver function tests, urine analysis, immunological studies) in PTS patients are generally normal. Cervical vertebrae and shoulder radiographs are usually normal in PTS patients. Shoulder pathologies which may cause pain and weakness such as impingement syndrome, adhesive capsulitis, etc. may be frequently confused and disregarded. In our case, noshoulder-related pathologywas found. In the differ-

ential diagnosis; cervical disc herniations, poliomyelitis, amyotrophic lateral sclerosis, herpes zoster, spinal cord or brachial plexus tumors and traumatic, compressive nerve injuries, myopathies, polymyalgia rheumatica and other rheumatologic diseases should also be considered [5]. The most useful study for diagnosis isindicated as electromyography. Although the electromyographic findings may be variable, the most important feature is the presence of acute denervation findings showing axonal neuropathy such as fibrillation and positive sharp waves [10]. Treatment of PTS is symptomatic and usually prognosis is good. The goals of treatment are determined as relieving pain, maintaining range of motion of the joints, restoring muscle strength and maximizing functional capacity of patient. There is no evidence of the superiority of any treatment. Corticosteroids and intravenous immunoglobulin in the early period of weakness has been suggested to prevent progression of disease, but its effect has not been proven [11].In our case, we applied methylprednisolone as pharmacologic treatment and physical medicine and rehabilitation program as nonpharmacologic treatment. As a result of the treatments, the patient's muscle strength was completely improved and the pain completely passed. Our case is similar to other cases in the literature but the importance of this case is its rarity. In addition the diagnosis of PTS was not considered enough in the differential diagnosis of shoulder pain and weakness as mentioned above. Therefore it is aimed to raise awareness of PTS in this case report.

CONCLUSION

PTS should be considered in the differential diagnosis of shoulder pain and weakness. Providing adequate information to the patient about the good prognosis of the disease will allow the treatment to proceed more positively. Although a special rehabilitation program is the most important parameter, we believe that corticosteroid therapy will be beneficial.

Informed consent

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

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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The European Research Journal 2020;6(4):362-364 Case Report

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A rare arrhythmia in the newborn: posterior fascicular ventricular tachycardia

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ABSTRACT

Arrhythmias are most frequently seen in the neonatal period. Left posterior fascicular ventricular tachycardia is quite rarely seen in children and infants. In this case report, we present a newborn patient and management of left posterior fascicular ventricular tachycardia.

Keywords: Arrythmia, fascicular ventricular tachycardia, cardioversion, neonate

The left posterior fascicular VT, which was firstly defined in 1979 by Zipes *et al*. [1], is an important cardiac arrhythmia with specific electrophysiological characteristics. This arrhythmia, which usually occurs in young adults who do not have a structural cardiac problem, is quite rarely seen in children and infants. In this case report, we present a patient with left posterior fascicular VT, and its management in the neonatal age group.

CASE PRESENTATION

The patient in our case report is a male infant born from a 29-year-old mother, and was admitted on postnatal 6th day due to tachycardia. In the electrocardiogram (ECG), the heart rate was 201-208/min, QRS: 85 ms, right bundle branch block and superior axle pattern were revealed, P waves could not be selected, and the posterior fascicular ventricular tachycardia was considered (Fig. 1). Patient's vital signs, other systemic examinations, blood electrolytes and thyroid function values were normal except for tachycardia. There was no response to parenterally-administered 0.75 mg adenosine. When the ejection fraction (EF) of the patient, whose heart rate could not be controlled despite the propranolol treatment, decreased to 56% in repeated echo, and normal sinus rhythm was obtained by performing synchronized cardioversion as 1 j/kg (Fig. 2). The patient was discharged by prescribing oral propranolol (4×0.25 mg/kg/day, max 3.5 mg/kg/dose); but was admitted to another pediatric clinic with a new tachycardia after 3 days. Because of not obtaining sinus rhythm despite 3 synchronized-cardioversions with 1 j/kg electrical dose, he was transferred to our clinic where amiodarone (5mg/kg/dose loading after 7-15 mcg/kg/min IV, 2×5-10 mg/kg/dose oral) was started for pharmacological cardioversion. The amiodarone treatment of the patient whose heart rhythm returned to normal within 45 minutes was discontinued. Oral sotalol (2×1 mg/kg/day, max 4 mg/kg/dose) treatment

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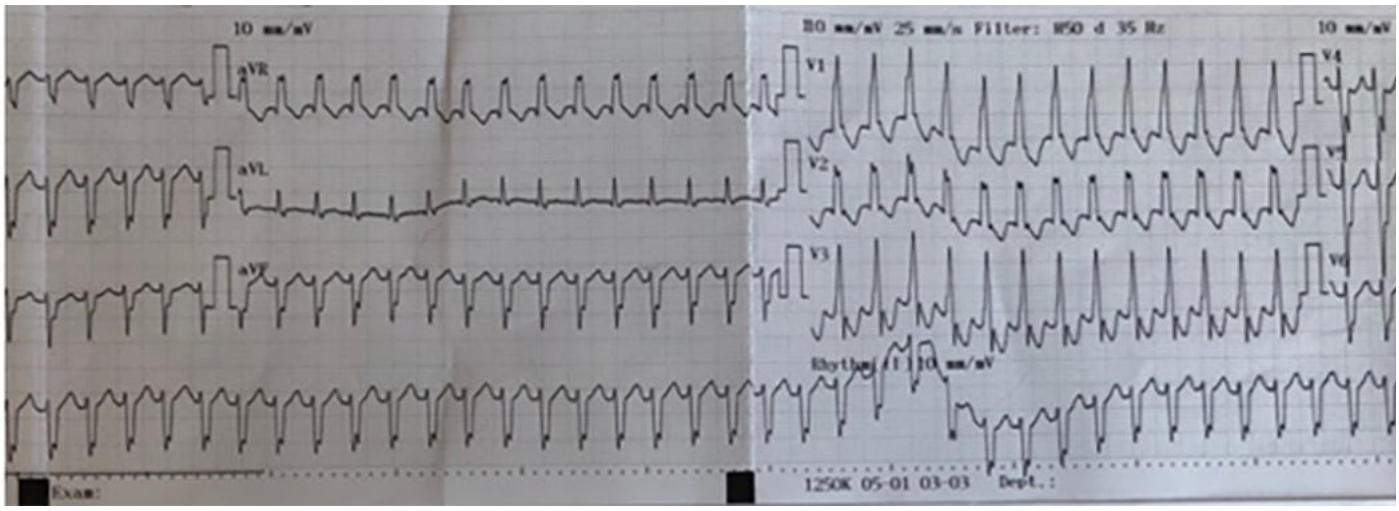

Fig. 1. **Electrocardiogram before cardioversion of the patient.**

was started. At the 72nd hour of the sotalol treatment, he had normal 24-hour rhythm Holter analysis, normal ECG (QTc: 320 ms), and was then discharged.

DISCUSSION

Arrhythmias during the neonatal period can easily escape from the eye due to the conditions seen in some arrhythmias such as the absence of clinical symptoms, difficulty in diagnosis, and improvement over time. In initial 10 days in life, 1-5% of the newborns have arrhythmia, which is generally a result of the continuation of fetal arrhythmia [2]. The clinical symptoms depend on the rate and duration of arrhythmias, which are categorized as benign or non-

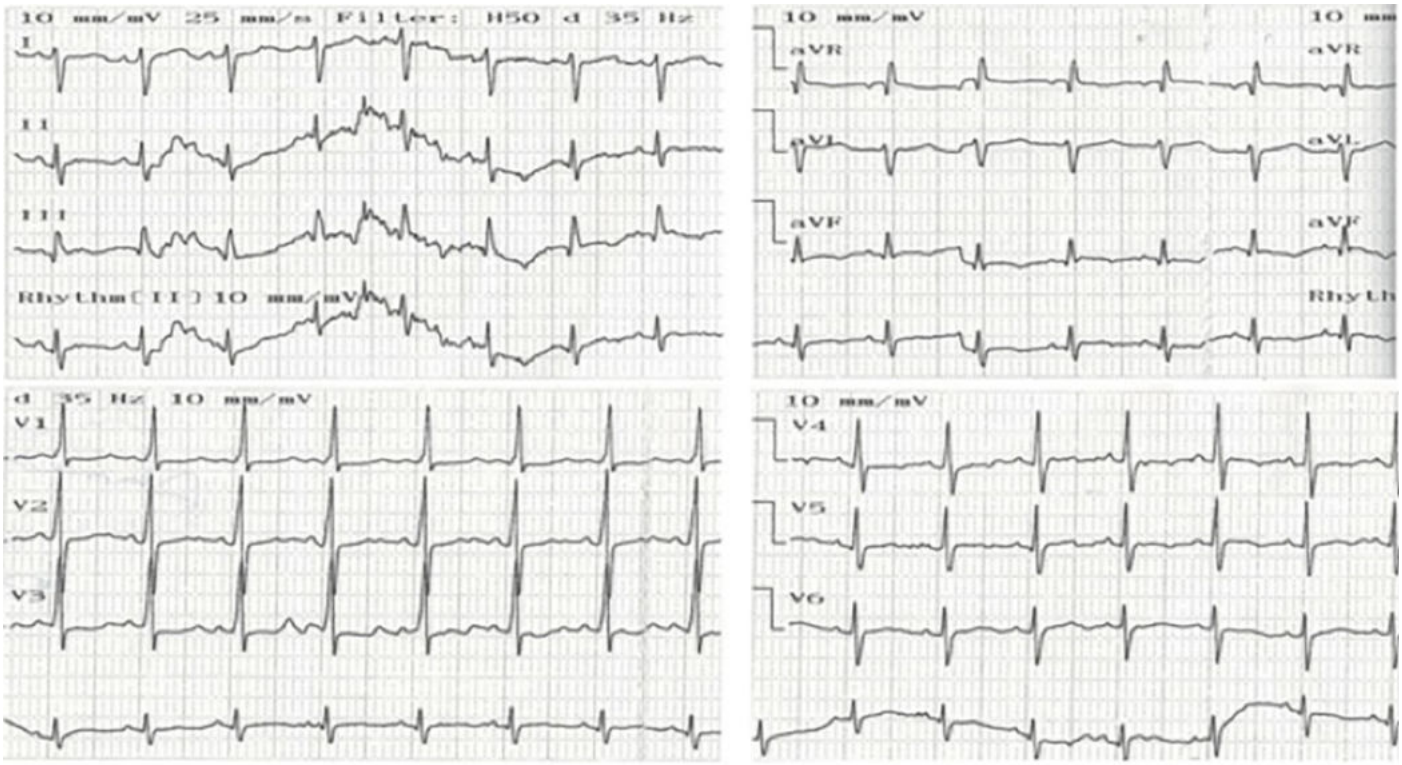

Fig. 2. **Electrocardiogram after cardioversion of the patient. Normal sinus rhythm.**

benign. Non-benign ones involve supraventricular tachycardia (SVT), atrioventricular conduction system disorders, ventricular tachycardia and fibrillation, long QT syndrome and electrolyte disturbance arrhythmias [3].

The left posterior fascicular VT is an important cardiac arrhythmia, which usually occurs in young adults who do not have a structural cardiac problem, is quite rarely seen in children and infants [1]. Arrhythmias are classified into three subtypes according to origin locations. Left posterior fascicular VT is manifested by right bundle branch block and left axis deviation. Left anterior fascicular VT is seen together with right bundle branch block and right axis deviation, and upper septal fascicular VT is associated with narrow QRS complex and normal axis. The most common type is posterior fascicular VT, which covers approximately 90% of cases, and our case was also in this type. The VT's ECG characteristic indicates widening of QRS with a bundle branch block pattern and atrioventricular dissociation. VT must be differentiated from other mechanisms that appear rarely in infants that also have wide QRS tachycardia; SVT/ atrial fibrillation included with bundle branch block, Mahaim tachycardia, aberrant SVT, SVT with anterograde conduction across an accessory pathway. We also administered adenosine to our patient in order to exclude both SVT differential diagnosis and adenosine-responsive VTs. Hypoxia, electrolyte disorders, acidosis, harmful substances used by mother, drugs given to the infant, myocarditis can be predisposing factors for neonatal arrhythmias. When an identifiable predisposing condition is absent, VT is often a finding that is benign. We could not detect a predisposing cause in our case, so we considered it as idiopathic VT. Treatment and prognosis of it are based on VT mechanism and pattern, the hemodynamic impact, and relevant conditions [4]. Performing synchronized cardioversion with electrical dose of 1 j/kg is necessary in cases which has high heart rate, prolonged arrhythmia and hemodynamic instability. In initial hospital admission of the patient, we also preferred synchronized cardioversion in our patient who did not respond to oral propranolol whose EF value was seen as decreased in echocardiography performed at early period, and we received reply. However, cardioversion was not effective at the patient's second admission. In clinically stable cases, adenosine may be administered to exclude possible branch block and aberrant SVT. If clinical signs are stable, intravenous lidocaine, esmolol and their combination with oral propranolol and flecainide, respectively, may be preferred. Calcium channel blockers are contraindicated in newborns.

CONCLUSION

If there is no response to treatment, the best choice is amiodarone. Discharge with beta-blockers is appropriate approach for patients whose attacks are under control. In the management of fascicular VT, catheter ablation is a curable treatment in fascicular even in infancy when the presence of medical treatment resistance [5].

Informed consent

Written informed consent was obtained from the patient's family for publication of this case report and any accompanying images.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Coping with the coronavirus (COVID-19) pandemic

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ABSTRACT

The global virus outbreak called COVID-19 has been one of the important breaking points in world history. COVID-19 is not only a physical disease affecting the whole world, but also an important issue in terms of community mental health, the effects of which will be understood in the long term. It is essential to explain the long-term and ongoing mental health effects of COVID-19 to take preventive steps. The aim of the present article was to review the impact of similar outbreaks in the past and to understand the potential impact on mental health through data from ongoing studies. Additionally, we summarized possible risk factors that may arise in infected people, healthcare professionals and the general population during COVID-19 outbreak.

Keywords: Covid-19, mental health, psychiatry, depression, anxiety, healthcare professionals

COVID-19 outbreak was a sudden pandemic for almost any country, society or family. With the advances in medicine, the use of antibiotics, vaccines and sanitation, the ever-decreasing deadly and infectious disease threat reappeared with the COVID-19 outbreak [1]. In the midst of an unusual infectious outbreak, fear and negative attitudes among people are understandable since being infected is not affected by any gender and socio-demographic situation and it is a potential risk for everyone.

Throughout history, outbreaks have had lasting and massive effects, from handover of dynasties to colonialism and even climate change. Many epidemics such as bubonic plague, Justinian plague, smallpox, Spanish flu, Asian flu, scarlet fever and rubella have left important trace in history and have significantly affected the course of events. In recent years, epidemic diseases such as SARS, MERS, bird flu, Swine flu, Ebola and new type coronavirus (Covid-19) spread rapidly in a short time. Covid-19, which was first seen in December 2019, infected three million people just in four months, causing the death of hundreds of thousands of people.

The earlier reactions to the attack of a virus, the source of which was still not fully understood, were denial, shock and surprise. Denial was initially a defense reaction that all societies had to deal with, reflecting not only ignorance but also the difficulty in accepting such kind of threat since every person on earth was under risk. Especially in the earlier stages of the pandemic, burying of the bodies quickly and randomly, and cremating of them collectively and brutally in the middle of the streets in some countries, were watched with horror by billions of people. Media portrayal has assisted to frighten both "those who were not afraid", and who were already anxious.

Kelly [2] had indicated that some preventive actions to control the virus may have negative effects on mental health of individuals. Due to lack of information, quarantine can be associated with frustration, fear of infection, boredom and anxiety. All schedules, projects, programs, short-medium-long-term plans

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were postponed to an uncertain date during the process we have been living. Stigmatization and financial problems also have increased the risk of potential mental health problems. Covid-19 caused mental health problems in two ways. First, the mental problems caused by the virus itself, and the second is the anxiety, panic and psychological problems associated with the pandemic. Covid-19 should be considered as not only a health crisis but also a mental health emergency. Initially, much less attention has been paid to the mental health consequences of the pandemic than other medical outcomes posed by the viral infection. However, when the pandemic ends; we will resume our normal life, but its psychological effects will probably last for months or even years.

Studies investigating the psychiatric effects of the outbreak on people are few and still ongoing. Therefore, it would be beneficial to examine the effects of past outbreaks or traumatic events on mental health in order to predict potential consequences of COVID-19 pandemic. This paper aims to review current and previous studies to explain the effects of COVID-19 on mental health.

Mental health impacts of COVID-19 on the general population and the infected patients

In China, a web-based cross-sectional survey revealed that prevalence of generalized anxiety disorder (GAD), depressive symptoms and poor sleep quality were 35.1%, 20.1% and 18.2% respectively during COVID-19 outbreak [3]. GAD and depressive symptoms were more common among participants younger than 35 years. According to American Psychiatric Association's national survey [4], about half of Americans (48%) were concerned about being infected by COVID-19. 40% of Americans were concerned about serious illness or death from COVID-19, while 62%of Americans were concerned about the possibility of their family members or loved ones getting COVID-19 [5]. These studies evaluate the psychological well-being and anxiety/depression levels that have been experienced over past 2 weeks. Unlike other studies, in Denmark results were compared with the previous surveys that had been conducted in 2016. This study showed that the psychological well-being of the general Danish population was negatively affected by the COVID-19 pandemic. When these studies are considered, it is understood that the epidemic might exert negative effects on general well-being of individuals, increase the risk of depression and anxiety.

In China, to examine the potential mental health problems related to quarantine, researchers obtained data from online survey and compared the quarantined and not quarantined groups [6]. High prevalence of mental health problems were found in both groups, however there was no significant difference between participants with or without quarantine. According to that study, mental health problems during this period were due to the effects of COVID-19 on daily life, not due to quarantine.

Zhang *et al*. [7] compared three different groups to evaluate the psychological distress across populations in Zhongshan, Guangdong China. COVID-19 infected patients who were recovered from illness, quarantined individuals and the general public were compared. Prevalence of depression comorbid with anxiety symptoms in the quarantined group were lower (8%) than that of the infected (21.1%) and the general public (22.4%). High prevalence of depression (29.2%) was found among patients who experienced COVID-19 infection. The prevalence of anxiety was not different among three groups. COVID-19 infected patients (19.3%) and general public (14.3%) had severe depression symptoms, infected patients and general public were more likely to have depressive mood, anxiety-like behaviors and somatic symptoms.

To evaluate the long-term effects of COVID-19, and whether the outbreak had changed the symptoms of generalized anxiety, post-traumatic stress disorder (PTSD) and depression over time, it had been investigated with the data obtained during the initial outbreak and four weeks later during the peak of the epidemic in China. In the first assessment, moderate to severe levels of anxiety, stress and depression were found in groups. Levels of stress, anxiety, depression, and PTSD symptoms of participants did not differ significantly over time [8].

Mental health of COVID-19 patients and health care workers

There are studies supporting the view that recent epidemics had severe effects on mental health of the infected patients. It is revealed that mental health problems have occurred among healthcare workers and patients who survived SARS epidemic [9] and

MERS epidemic [3]. When the long-term effects of the SARS epidemic had been analyzed, it was observed that the prevalence of depressive disorders and PTSD has increased after outbreak [3, 10].

Infected people may have feelings of guilt, anxiety and hopelessness combined with physical problems of infection and long periods of hospitalization[2]. Complex emotional processes are likely to occur due to the feelings of guilt, despair, loss and inability to visit patients or limited funerals. In this emotionally charged environment, psychological support is vital both at the time of death, illness and in the future. Mental health workers should be able to reach to infected and quarantined patients to get appropriate mental health services during COVID 19 outbreak.

In addition to infected patients, the mental health of health workers combatting with the virus is also at significant risk. Especially, health care personnel working in the intensive care units and the emergency departments are at risk for psychological symptoms. During SARS epidemic in Singapore, psychiatric symptoms were seen 27% of health care workers [10], and PTSD symptoms arised among health care workers during MERS outbreak in Korea. Correspondingly, during Ebola outbreak in Congo, health care workers reported high levels of anxiety and fear of being stigmatized [2].

During COVID-19 outbreak, Lai *et al*. [13] aimed to explore the healthcare workers' psychiatric symptoms. It has been found that the frequency of depression, anxiety, insomnia and distress symptoms were significantly higher among health-care workers who treated COVID-19 patients. Especially health care professionals were exposed patients with COVID-19, experienced higher rates of depression and anxiety compared to those without exposure [14]. Furthermore, the study revealed significantly higher levels of anxiety and depression experienced by pediatric health personnel during the COVID-19 outbreak in China Guiyang.

A similar study had been conducted in China, to examine the work stress of nurses who were working against COVID-19 [15]. The study revealed that stress load of nurses was significantly high and they were experiencing considerable stress during that period of COVID-19 [15]. Li *et al*. [16] compared general public, medical workers, and medical workers that directly work with COVID-19 patients according to their vicarious traumatization level. Study revealed that vicarious traumatization levels of general public and non-front-line nurses were higher than the nurses that directly deal with infected patients. This study reveals that, not only health care workers but also general population are at risk for traumatizing experiences even they are living in isolation.

Mental health risks of COVID-19 on pre-existing mental health problems and vulnerable groups

While the mental problems of healthcare workers and infected patients are primarily considered, other groups should also be explored to identify vulnerable populations and risk groups. By this way, it may be possible to take protective measures and track long-term effects. When outbreaks occur, people with mental health disorders are often more vulnerable to infections for several reasons [17]. Cognitive impairment, less risk awareness and less personal protection efforts of people with mental disorders may increase the risk of infectious diseases in everyday life and in psychiatric clinics. Another potential risk factor is that infected people with mental disorders may have low awareness to seek treatment on time or they may have difficulty in getting services due to their mental condition. For some patients with their own idiosyncratic concerns, they may have trouble grasping the reality when a true threat really exists. Compared with the general population, people with mental health disorders may be more affected by emotional conditions caused by COVID-19 outbreak, and their condition may worsen. Therefore, the disease caused by COVID-19 is also a risk factor for psychiatric patients, as the life expectancy and general health outcomes of people with mental illness are lower than general population. On the other hand, many people with mental disorders regularly receive outpatient treatment. However, with the countries' travel restrictions and quarantine procedures, regular doctor checks may become difficult and disrupt treatment processes.

During this period, for some of the groups who resume their consultations through online therapy, social isolation and online therapy contain risk factors in itself. Telepsychiatry can be challenging in paranoid patients, individuals with suicide risk, substance abuse, individuals with a tendency to violent behaviors, and psychotic patients receiving regular medication [18].

It is proposed that individuals with suicide risk require special attention during the pandemic period [19]. There are some studies showing that suicide rates increased in the U.S. during the 1918-19 flu outbreak and among older people in Hong Kong during severe acute respiratory syndrome (SARS) outbreak in 2003 [20]. Suicide risk increases when social isolation and loneliness occurs, so during this outbreak, current situation increases suicide risk especially for individuals who are grieving due to loss of a loved one [19, 21].

It may be important to understand the COVID-19 process on children with different developmental characteristics. One of such groups that might be in risk during COVID-19 outbreak is children with ADHD. In most countries, schools were closed and students were expected to attend online education. It is anticipated that children with ADHD may face visible difficulties during this period due to the loss of the daily routine, interpersonal and social interaction. According to the results of the first study focusing on children with ADHD during the COVID-19 outbreak, the behaviors of children with ADHD have significantly deteriorated during outbreak compared to their normal state [7]. Additionally, negative correlations were found between the ADHD symptoms and increased online education and working time. According to this cross-sectional research, ADHD symptoms decreased with longer working time.

CONCLUSION

Ongoing studies have been trying to explore the potential effects of COVID-19 on population mental health. COVID-19 may have an aggravating effect on mental health of populations during and after the pandemic. Therefore, risk factors should be determined for comprehensive interventions in the future, such as poor mental health before the outbreak, being infected or having infected family members, separation from family and social support, low economic conditions. Thus far, under strict infection treatment procedures, unless mandatory situations for psychiatrists, psychologists and social workers, it was difficult to enter isolation services for patients. Therefore, front-line health workers were the main personnel, who also provided psychological support, in addition to their workload [22]. However, the importance and position of psychological support will be more obvious in the near future. Overall, these extraordinary times are thought to make many people vulnerable to mental health problems and risky behaviors and these mental health problems are predicted to be more apparent after the pandemic.

Conflict of interest

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Beta endorphins - molecules of therapeutics

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ABSTRACT

Endorphins are endogenous morphine, neuropeptides produced in the pituitary gland. There are three types of endorphins beta-endorphins, enkephalins, and dynorphins. Beta-endorphins are an abundant endorphins synthesized and stored in the anterior pituitary gland; it is a precursor of POMC (Proopiomelanocortin). Beta-endorphins has got various mechanisms of actions such as anti-inflammatory activity, analgesic activity, stress buster activity, and immune stimulatory activity can be used to treat various diseases such as chronic inflammatory diseases such as heart disease, Alzheimer's disease, cancer, auto-immune disease, diabetes mellitus, and aging. This article highlights about the basic research findings of beta-endorphins and mechanisms of actions in management of various diseases.

Keywords: NF-KB, STAT-3, Cortisol, ACTH, Noradrenaline

Endorphins are endogenous morphine, neuropeptides produced in pituitary gland, response to stress and pain. There are three types of endorphins beta endorphins, enkephalins, and dynorphins binds to mu (μ), kappa (k), and delta (Ò) receptors situated on nervous system and immune cells. Beta-endorphins are an abundant endorphins, more potent than morphine, synthesized and stored in the anterior pituitary gland, it is precursor of POMC (pro-opiomelanocortin). Endorphin receptors are increased during stress such as inflammation, binds abruptly with endorphins.

Holistic is a whole person healing. Human body works as a whole. Instead of considering human body as a whole, if we consider as a parts in treating any disease with reductionist chemical drugs yield better results without adverse effects.

Adverse drug reactions is a major killer in the present world, cancer is a major threat to mankind. Majority of cancers more than 90% of all cancers are due to external environmental factors such as tobacco, alcohol, and infectious agents (such as HBV, EBV). Human environment is the most important factor in any disease including cancer. Important part of the human environment is human mind; human mind is a human consciousness. Chronic psychological stress is one of the important factors for many diseases including human cancer. Cancer cells works exactly like normal cells. "I do not know any treatment how to kill the cancer cells without killing normal cells" said by novel laureate Albert Szent gyorgi. Advanced cancer treatment modalities such as, surgery, radiotherapy, chemotherapy failed to improve the prognosis of the cancer with increasing morbidity, adverse drug reactions, and decreased survival rate. Endorphins are produced during mindful meditation, massage, pranayama, pranic healing, intense physical exercise creates a psychological relaxed state known as 'Runner's high', love, tender care, music therapy, acupuncture, sympathy and empathy in caring the patient [1-5].

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MECHANISMS OF ACTIONS OF BETA-ENDORPHIN

In inflammatory state, recruitment of immune cells to the site of inflammation by chemokine's produces endorphins. Binding of endorphins to the receptors of peripheral nerves results in inhibition of substance P, a neuro transmitter of pain and inflammation, produce IL-10, IFNϒ anti inflammatory cytokines to reduce inflammation. In the PNS, binding of beta endorphin to the μ receptors situated on the peripheral nerves results in inhibition of substance P, a neurotransmitter of pain and inflammation. In the CNS, binding of beta endorphin to the mu receptors situated on the central nervous system results in inhibition of GABA inhibitory neurotransmitter, produce dopamine neurotransmitter involved in analgesic activity, stress buster activity, euphoria, and tranquillity of mind, cognitive development, self reward, and addiction. Endorphin receptors are situated on most innate and adoptive immune cells. Binding of beta - endorphins to the mu receptors situated on innate and adoptive cella such as neutrophils, macrophages, mast cells, dendritic cells, natural killer cells, T cells, B cells, results in activation of immune cells(immune stimulatory activity) release opsonin, granzyme-B, interferon ϒ and antibodies involved in antibacterial activity, antiviral activity, antitumor activity and anti inflammatory activity. Beta endorphins inhibits chronic psychological stress induced sympathetic nervous system activity and activation of parasympathetic nervous system activity of ANS through inhibition of HPA- axis mediated release of neuropeptides such as cortisol, ACTH, and nor adrenaline inhibit inflammatory mediators such as IL-1β, IL-6, TNFα, and COX2, which inhibits NFKB and STAT-3 key transcription factors involved in chronic inflammatory diseases such as heart disease, Alzheimer's disease, cancer, auto immune disease, infectious diseases and diabetes mellitus, aging.

Beta endorphins inhibits chronic psychological stress induced activation of NF-KB a key transcription factor of induced inflammatory mediators involved in conversion of TH1 lymphocytic type to TH2 lymphocytic type, mediated by IL-4, STAT-6 transcription factor, release IL-4, IL-5, IL-13, pro inflammatory cytokines involved in chronic inflammation, tissue damage, immune modulation. Growth factors such as EGF, FGF, VEGF, involved in cell proliferation, cell survival. Altered induced regulatory T cells (ATregs) formed from TH-1 cells mediated by TGF-β inflammatory mediator release IL-2, IL-3, IL-4, IL-5, IL-10, IL-17, pro-inflammatory cytokines involved in immune modulation, otherwise normally regulatory T cells (nTregs) involved in self-tolerance and immune homeostasis. Proteolytic enzymes such as UPA (Urokinase plasminogen activator), matrix metalloproteases (MMP's) 2,9 involved in tissue damage, all these changes leads to autoimmune diseases. Beta-endorphin inhibits chronic psychological stress induced neuropeptide's activate inflammatory mediators such as IL-1 β, TNFα, COX2 pro-inflammatory cytokines activate NFKB a key transcription factor and IL-6, EGF, FGF, PDGF, pro-inflammatory mediators activates STAT-3 transcription factor, both transcription factors work together involved in cell proliferation by activation of cell cycle regulatory proteins such as cyclin D, E and apoptosis (cell survival) by activation of anti apoptotic proteins such as BCL-XL, BCL-2, angiogenesis by IL-8, COX-2, VEGF, Invasion and metastasis by MMP's 2,9 all these changes lead to tumour progression.

Beta endorphins inhibits chronic inflammatory mediators induced activation of NF-KB a key transcription factor involved in tumour progression, which antagonise P53 tumour suppressor gene, a guardian of the genome mutated in more than 50% of all cancers by inflammatory mediators such as NO (nitric oxide), ROS, RNS, free radicals, AID (activation induced cytidine deaminase) enzyme expressed by NF-KB a key transcription factor. Beta endorphins express epithelial E-cadherin helps in cell adhesion, loss of epithelial E-cadherin mediated epithelial to mesenchymal transition induced tumour invasion. Beta endorphins delay aging by lengthening telomeres, which otherwise shortened with aging. Another mechanism of delay aging by inhibiting ROS, RNS free radicals from inflammatory cells such as neutrophils, macrophages, dendritic cells during oxidative stress via NADPH oxidase pathway involved in cell aging, tissue damage, DNA damage, gene mutation and cell death (1-9). Beta endorphins are an abundant endorphin useful in natural holistic preventive, therapeutic, health promotive, and palliative treatment of various

diseases such as heart disease, Alzheimer's disease, cancer, infectious diseases, aging, auto immune disease and diabetes mellitus without adverse effects and inexpensive by its immune stimulatory activity, stress buster activity, analgesic activity and anti -inflammatory activity.

CONCLUSION AND FUTURE PERSPECTIVE

Endorphins are endogenous morphine, neuropeptides produced in the pituitary gland. Beta-endorphins are an abundant endorphins involved in treatment of various diseases by its analgesic activity, anti-inflammatory activity, stress buster activity, and immune-stimulatory activity without adverse effects and inexpensive. Thorough understanding of beta-endorphins, types, mechanisms of actions, duration of action, and prognosis related to disease helpful for future therapeutic purpose.

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